(19) JAPANESE PATENT OFFICE

PATENT ABSTRACTS OF JAPAN

(11) Publication number: **11171848 A**
(43) Date of publication of application: **29.06.1999**

(51) Int. Cl **C07C237/40**
A61K 31/00, A61K 31/00, A61K 31/16, A61K 31/19, A61K 31/38,
A61K 31/44, A61K 31/445, C07C255/58, C07C311/46, C07C311/51,
C07D213/56, C07D213/80, C07D295/14, C07D333/24, C07D333/38

(21) Application number: **10270721**
(22) Date of ¿0Q **25.09.1998**
(30) Priority: **26.09.1997 JP 09277942**

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NAKAMURA TAKASHI

(54) **AROMATIC AMIDE DERIVATIVE**

(57) Abstract:

PROBLEM TO BE SOLVED: To obtain the subject new compound having Acetyl-CoA Carboxylase (hereafter, referred to as ACC) inhibitory activity, and useful for the treatment of viseral adiposis syndrome as a risk factor of geriatric diseases such as myocardial infarction, cerebral infarction and diabetes.

SOLUTION: This new compound is an aromatic amide derivative of formula I (R^1 and R^2 are each H, a 1-12C alkyl, aromatic hydrocarbon group, aromatic heterocyclic group or the like; R^3 is H, a substituted amino, 1-12C alkyl, 2-12C alkenyl or the like; Y is CH=CH, N=CH, or the like; R^4 is an acidic functional group; ring A is an aromatic hydrocarbon group, aromatic heterocyclic group or cyclic alkyl), e.g. 2-[2-(3-trÀXRURP HAylphenylamino)benzamido]benzoic acid. The amide derivative of formula I is obtained, for example, by condensation reaction between an amino compound of formula II and a carboxylic acid compound of formula III in the presence of a condensation agent and a base in an inert solvent.

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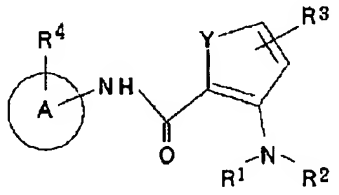
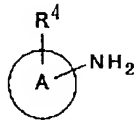


I



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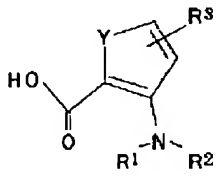

III

(19)日本国特許庁（ＪＰ）　(12) **公開特許公報**（Ａ）　(11)特許出願公開番号

特開平11－171848

(43)公開日　平成11年(1999)６月29日

(51)Int.Cl.[6]	識別記号	ＦＩ	
Ｃ０７Ｃ 237/40		Ｃ０７Ｃ 237/40	
Ａ６１Ｋ 31/00	６０３	Ａ６１Ｋ 31/00	６０３Ｌ
			６０３Ｎ
	６０６		６０６Ｆ
31/16		31/16	

審査請求　未請求　請求項の数８　ＯＬ　（全 72 頁）　最終頁に続く

(21)出願番号　特願平10－270721

(22)出願日　平成10年(1998)９月25日

(31)優先権主張番号　特願平9－277942

(32)優先日　平９(1997)９月26日

(33)優先権主張国　日本（ＪＰ）

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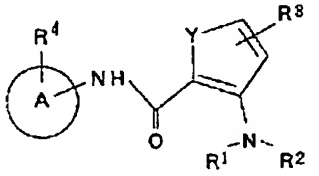
(54)【発明の名称】　芳香族アミド誘導体

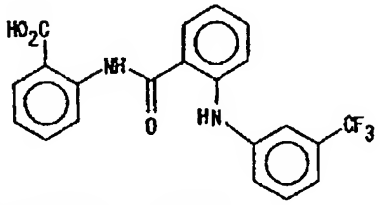
(57)【要約】　（修正有）

【課題】　心筋梗塞、脳梗塞、糖尿病等の成人病のリスクファクターとなる内臓脂肪症候群の治療に有効なＡＣＣ活性阻害剤としての新規な芳香族アミド誘導体の提供。

【解決手段】　一般式

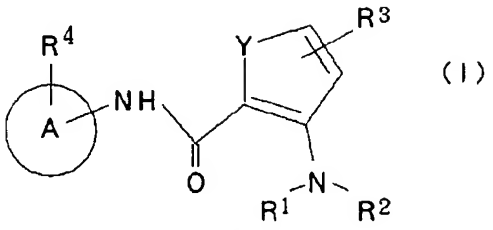


具体的には、例えば



で表される芳香族アミド誘導体。

【特許請求の範囲】
【請求項１】　一般式
【化１】



（Ⅰ）

で表される芳香族アミド誘導体
（式中、R^1 及びR^2 は水素原子、置換もしくは無置換のC_1 ～C_{12}のアルキル基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を示し、更に、このR^1 およびR^2 は、同時に水素原子となることはなく、またそれらが結合している窒素原子と一体になり結合して５～７員の環構造を形成することができ、
R^3 は水素原子、置換アミノ基、置換もしくは無置換のC_1 ～C_{12}のアルキル基、置換もしくは無置換のC_2 ～C_{12}のアルケニル基、置換もしくは無置換のC_2 ～C_{12}のアルキニル基、置換もしくは無置換のC_1 ～C_{12}のアルコキシ基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を示し、
Yは－ＣＨ＝ＣＨ－，－Ｎ＝ＣＨ－，－ＣＨ＝Ｎ－で表される基、硫黄原子または酸素原子を示し、
R^4 は酸性官能基を示し、
環Aは置換もしくは無置換の芳香族炭化水素基、置換もしくは無置換の芳香族複素環基または置換もしくは無置換の環状アルキル基を示す。）。
【請求項２】　環Aが１，２位に置換位置を有する芳香族炭化水素基、１，２位に置換位置を有する芳香族複素環基または１，１位に置換位置を有する環状アルキル基である請求項１記載の芳香族アミド誘導体。
【請求項３】　R^3 が置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 アルキル基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_2 ～C_4 アルケニル基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_2 ～C_4 アルキニル基、または置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 アルコキシ基であり、R^1 が置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 のアルキル基である請求項２記載の芳香族アミド誘導体。
【請求項４】　R^3 が無置換のC_5 ～C_{12}アルキル基、無置換のC_5 ～C_{12}アルケニル基、無置換のC_5 ～C_{12}アルキニル基または無置換のC_5 ～C_{12}アルコキシ基であり、R^1 が置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 のアルキル基である請求項２記載の芳香族アミド誘導体。
【請求項５】　R^3 が水素原子であり、R^1 が置換もしくは無置換の芳香族炭化水素基、置換もしくは無置換の芳香族複素環基、または置換もしくは無置換のC_4 ～C_{12}のアルキル基である請求項２記載の芳香族アミド誘導体。
【請求項６】　酸性官能基がカルボキシル基である請求項１記載の芳香族アミド誘導体。
【請求項７】　酸性官能基が一般式R^5 ＣＯＮＨＳＯ$_2$ーで表される基である請求項１記載の芳香族アミド誘導体（式中、R^5 は置換もしくは無置換のC_1～C_{12}のアルキル基、芳香族炭化水素基、置換アミノ基または置換もしくは無置換のC_1 ～C_{12}のアルコキシ基である。）。
【請求項８】　請求項１ないし７のいずれかに記載の芳香族アミド誘導体またはその薬理学的に許容される塩を有効成分とする医薬。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、芳香族アミド誘導体に係り、詳細にはAcetyl-CoA Carboxylase（以下、ＡＣＣと略記する場合もある）阻害活性を有する新規な芳香族アミド誘導体に関する。
【０００２】
【従来の技術】近年、内臓脂肪組織への中性脂肪、特にトリグリセリドの過剰蓄積は、高脂血症、高血圧症、動脈硬化症、心筋梗塞、耐糖能異常等の様々な疾患の主要なリスクファクターであることが明らかとなってきた。すなわち、内臓脂肪組織においては脂肪酸合成が活性化しており、この脂肪酸は門脈内に放出されるとインシュリン抵抗性を亢進し、さらに肝臓内に取り込まれトリグリセリドの原料として利用され、血漿中に放出されて高トリグリセリド血症を来すと考えられている。
【０００３】一方、ＡＣＣはAcetyl-CoAよりMalonyl-CoA の合成を触媒する酵素であり、長鎖脂肪酸の生合成における律速酵素である。また、ＡＣＣによりAcetyl-CoAから合成されたMalonyl-CoA 自体は、遊離長鎖脂肪酸のエネルギー源としての消費に関与するCarnitine acyltransferase を制御していることが知られている。さらに、内臓脂肪組織における脂肪酸合成の活性化は、ＡＣＣの活性化が関与していると考えられている。したがって、ＡＣＣ活性を阻害する薬剤は、生体内において長鎖脂肪酸の生合成を阻害すると同時に代謝を促進することにより生体内における長鎖脂肪酸量を減少させ、結果としてトリグリセリドの生合成を抑制することとなり、内臓脂肪の蓄積に基づく様々な疾患の治療および予防薬と

しての可能性を有する。

【0004】

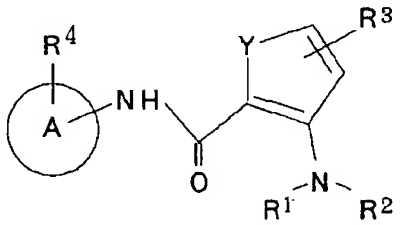
【発明が解決しようとする課題】本発明者らはかかる観点より、心筋梗塞、脳梗塞、糖尿病等の成人病のリスクファクターとなる内臓脂肪症候群の治療に有効なＡＣＣ活性阻害剤の探索を目的とし、鋭意検討した結果、下記一般式（Ｉ）で表される芳香族アミド誘導体に優れたＡＣＣ阻害活性が認められることを新規に見いだし本発明を完成した。したがって、本発明は新規な芳香族アミド誘導体およびその塩を提供することを課題とし、またこれらの化合物を有効成分とする医薬、特にＡＣＣ活性阻害剤を提供することを課題とする。

【0005】

【課題を解決するための手段】かかる課題を解決するために、本発明は一般式

【0006】

【化2】



（Ｉ）

【0007】（式中、R^1 及びR^2 は水素原子、置換もしくは無置換のC_1 ～C_{12}のアルキル基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を示し、更に、このR^1 およびR^2 は、同時に水素原子となることはなく、またそれらが結合している窒素原子と一体になり結合して５～７員の環構造を形成することができ、R^3 は水素原子、置換アミノ基、置換もしくは無置換のC_1 ～C_{12}のアルキル基、置換もしくは無置換のC_2 ～C_{12}のアルケニル基、置換もしくは無置換のC_2 ～C_{12}のアルキニル基、置換もしくは無置換のC_1 ～C_{12}のアルコキシ基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を示し、Ｙは－ＣＨ＝ＣＨ－，－Ｎ＝ＣＨ－，－ＣＨ＝Ｎ－で表される基、硫黄原子または酸素原子を示し、R^4 は酸性官能基を示し、環Ａは置換もしくは無置換の芳香族炭化水素基、置換もしくは無置換の芳香族複素環基または置換もしくは無置換の環状アルキル基を示す。）で表される芳香族アミド誘導体およびその塩を提供する。

【0008】

【発明の実施の形態】本発明により提供される前記一般式（Ｉ）で示される芳香族アミド誘導体はこれまで知られていなかった新規な化合物であり、かつこれらの化合物にＡＣＣ活性阻害作用があることも全く知られていなかったものである。しかしながら　後記する薬理試験の結果から明らかなように、これら化合物には、優れたＡＣＣ活性阻害作用があることが判明した。したがってこれら化合物は、特に、心筋梗塞、脳梗塞、糖尿病等の成人病のリスクファクターとなる内臓脂肪症候群の治療に有効なＡＣＣ活性阻害剤として極めて有用なものである。しかして、本発明はその別の態様として、前記一般式（Ｉ）で表される芳香族アミド誘導体またはその塩を有効成分とする医薬をも提供するものである。

【0009】以下に、本発明が提供する芳香族アミド誘導体について更に詳細に説明していくが、本明細書中において「C_1 ～C_{12}のアルキル基」としては、直鎖状、分枝鎖状または環状のいずれでもよく、メチル、エチル、ｎ－プロピル、１－メチルエチル、シクロプロピル、ｎ－ブチル、２－メチルプロピル、１－メチルプロピル、１，１－ジメチルエチル、シクロブチル、ｎ－ペンチル、１－メチルブチル、２－メチルブチル、３－メチルブチル、シクロペンチル、２，２－ジメチルプロピル、ｎ－ヘキシル、１－メチルペンチル、２－メチルペンチル、４－メチルペンチル、１－エチルブチル、２－エチルブチル、３，３－ジメチルブチル、シクロヘキシル、ｎ－ヘプチル、５－メチルヘキシル、４，４－ジメチルペンチル、シクロヘプチル、１－メチルヘキシル、２－メチルヘキシル、１－プロピルブチル、２－エチルペンチル、シクロヘキシルメチル、１，１－ジエチルプロピル、ｎ－オクチル、６－メチルヘプチル、シクロオクチル、１－メチルヘプチル、１－エチルヘキシル、５，５－ジメチルヘキシル、２－シクロヘキシルエチル、ｎ－ノニル、１－メチルオクチル、７－メチルオクチル、６，６－ジメチルヘプチル、ｎ－デシル、１－メチルノニル、８－メチルノニル、７，７－ジメチルオクチル、ｎ－ウンデシル、１－メチルデシル、９－メチルデシル、８，８－ジメチルノニル、ｎ－ドデシル、１－メチルウンデシル、１０－メチルウンデシル、５－メチルウンデシル、９，９－ジメチルデシル等を例示することができ、これらのアルキル基には更に種々の置換基が置換されていてもよい。そのような置換基としては、塩素、臭素、ヨウ素、フッ素等のハロゲン原子、ニトロ基、アミノ基、シアノ基、水酸基、アルコキシ基、チオール基、フェニル、ナフチル等の芳香族炭化水素基、チエニル、フリル、ピリジル等の芳香族複素環基を例示することができる。またこれらの芳香族炭化水素基および芳香族複素環基には、更に前記ハロゲン原子、アルキル基、アルコキシ基、ニトロ基、アミノ基、シアノ基、水酸基、チオール基等の置換基を有することもできる。

【0010】また、「置換もしくは無置換の芳香族炭化水素基」とは、単環式または多環式であり、さらに環上に１個以上の種々の置換基を有していてもよい芳香族炭化水素基をいい、例えばフェニル、メチルフェニル、ジメチルフェニル、メトキシフェニル、ジメトキシフェニル、ニトロフェニル、ジニトロフェニル、クロロフェニル、ジクロロフェニル、ブロモフェニル、ジブロモフェ

ニル、ヨードフェニル、フルオロフェニル、トリフルオロメチルフェニル、アミノフェニル、ヒドロキシフェニル、メルカプトフェニル、シアノフェニル、α－ナフチル、β－ナフチル基等を挙げることができる。

【００１１】「置換もしくは無置換の芳香族複素環基」とは、環構成原子として窒素原子、硫黄原子、酸素原子等の複素原子を少なくとも１以上含む５員環または６員環の基であり、これらはベンゼン環と縮合していてもよく、さらに環上に１個以上の種々の置換基を有していてもよく、例えば、ピリジル、フリル、チエニル、インドリル、キノリル、イソキノリル、ベンゾフラニル、ベンゾチエニル、イミダゾリル、ベンズイミダゾリル、チアゾリル、オキサゾリル、ピラゾリル、ピリミジル、ピラジル、イソオキサゾリル、イソインドリル、ピロリル等を挙げることができる。

【００１２】「C_2 ～C_{12}のアルケニル基」は、直鎖状または分枝鎖状のいずれでもよく、１－メチル－１－プロペニル、１－メチル－２－プロペニル、２－メチル－２－プロペニル、エテニル、１－メチルエテニル、１－プロペニル、２－プロペニル、１－ブテニル、２－ブテニル、２－ペンテニル、１－ペンテニル、１，３－ブタンジエニル、３－メチルブテニル、１－ヘキセニル、２－ヘキセニル、３，３－ジメチル－１－ブテニル、４，４－ジメチル－１－ペンテニル、１，３－ペンタジエニル、１，３－ヘキサジエニル、ヘプテニル、オクテニル、２－シクロヘキシルエテニルノネニル、デセニル、ウンデセニル、ドデセニル等を例示することができ、これらのアルケニル基には更に種々の置換基が置換されていてもよい。この置換基としては、前記C_1 ～C_{12}のアルキル基で例示した置換基と同一の基を挙げることができる。

【００１３】「C_2 ～C_{12}のアルキニル基」としては、直鎖状または分枝鎖状のいずれでもよく、１－プロピニル、２－プロピニル、１－メチル－２－プロピニル、１－エチル－２－プロピニル、エチニル、１－ブチニル、２－ブチニル、１，３－ブタジイニル、１－ペンチニル、２－ペンチニル、１，３－ペンタジイニル、１－ヘキシニル、２－ヘキシニル、１，３－ヘキサジイニル、３，３－ジメチル－１－ブチニル、ヘプチニル、オクチニル、シクロヘキシルエチニル、ノニイル、デシニル、ウンデシニル、ドデセニル等があげられ、これらの基には更に種々の置換基が置換されていてもよい。この置換基としては、前記C_1 ～C_{12}のアルキル基で例示した置換基と同一の基を挙げることができる。

【００１４】また、「C_1 ～C_{12}のアルコキシ基」とは、アルキル基が上記の意味を有するアルキル置換オキシ基を意味し、具体的には、メトキシ、エトキシ、ｎ－プロポキシ、１－メチルエトキシ、ｎ－ブトキシ、２－メチルプロポキシ、１－メチルプロポキシ、２－メチル－２－プロポキシ、１，１－ジメチルエトキシ、ｎ－ペンチルオキシ、３－メチルブトキシ、１－エチルプロポキシ、ｎ－ヘキシルオキシ、３，３－ジメチルブトキシ、ヘプチルオキシ、４－メチルペントキシ、シクロヘキシルメトキシ、オクチルオキシ、ノニルオキシ、デシルオキシ、ウンデシルオキシ、ドデシルオキシ等を例示することができる。またこれらのアルキル基には更に種々の置換基が置換されていてもよい。この置換基としては、前記C_1～C_{12}のアルキル基で例示した置換基と同一の基を挙げることができる。

【００１５】また「酸性官能基」とは水酸基、メルカプト基、ヒドロキサム酸基、カルボキシル基、ホスホノ基、スルホ基、スルフィノ基、スルフェノ基、チオカルボキシル基、または、これらのアミド、Ｎ－置換アミド、Ｎ－アシルアミドを意味する。Ｎ－アシルアミド基としては、例えば一般式R^5 $CONHSO_2$ －で表される基（式中、R^5 は置換もしくは無置換のC_1 ～C_{12}のアルキル基、芳香族炭化水素基、置換アミノ基または置換もしくは無置換のC_1 ～C_{12}のアルコキシ基である。）などを挙げることができる。R^5 の置換アミノ基としては、前記置換もしくは無置換のC_1 ～C_{12}のアルキル基、置換もしくは無置換のC_2 ～C_{12}のアルケニル基、置換もしくは無置換のC_2 ～C_{12}のアルキニル基、置換もしくは無置換のC_1 ～C_{12}のアルコキシ基、置換もしくは無置換の芳香族炭化水素基、または置換もしくは無置換の芳香族複素環基が、窒素原子に１ないし２置換したアミノ基であり、さらに置換基は結合する窒素原子と一体となり１－ピロリジニル基、ピペリジノ基、１－ピペラジニル基、モルホリノ基、チオモルホリノ基、１－パーヒドロアゼピニル基等のヘテロ原子を含む５～７員の飽和複素環構造を形成することもできる。

【００１６】酸性官能基としては、例えばカルボキシアミド、ホスホンアミド、スルホンアミド、スルフィンアミド、スルフェンアミド、チオカルボシサミド、Ｎ－ベンゾイルカルボキシアミド、Ｎ－フェニルカルボキシアミド、Ｎ－ベンゾイルスルホンアミド、Ｎ－（３－ベンジルオキシベンゾイル）スルホンアミド、Ｎ－（４－トリフルオロメチルベンゾイル）スルホンアミド、Ｎ－ベンジルスルホンアミド、Ｎ－フェニルスルホンアミド、Ｎ－（４－ニトロベンゾイル）スルホンアミド、Ｎ－ベンゾイルホスホンアミド、Ｎ－ベンゾイルスルフィンアミド、Ｎ－ベンゾイルチオカルボキシアミド、Ｎ－アセチルスルホンアミド、Ｎ－プロパノイルスルホンアミド、Ｎ－（２－メチル）プロパノイルスルホンアミド、Ｎ－ブタノイルスルホンアミド、Ｎ－ヘキサノイルスルホンアミド、Ｎ－デカノイルスルホンアミド、Ｎ－ドデカノイルスルホンアミド、Ｎ－（２，２－ジメチル）プロパノイルスルホンアミド、Ｎ－（２－シクロヘキシル）アセチルスルホンアミド、Ｎ－フェニルオキシカルボニルスルホンアミド、Ｎ－ベンジルオキシカルボニルスルホンアミド、Ｎ－メトキシカルボニルスルホンアミ

ド、N－エトキシカルボニルスルホンアミド、N－ブトキシカルボニルスルホンアミド、N－ヘキシルオキシカルボニルスルホンアミド、N－（2－メチル）プロポキシカルボニルスルホンアミド、N－（2，2－ジメチル）プロポキシカルボニルスルホンアミド、N－オクチルオキシカルボニルスルホンアミド、N－デシルオキシカルボニルスルホンアミド、N－ドデシルオキシカルボニルスルホンアミド、N－フェニルアミノカルボニルスルホンアミド、N－ベンジルアミノカルボニルスルホンアミド、N－メチルアミノカルボニルスルホンアミド、N－エチルアミノカルボニルスルホンアミド、N－ブチルアミノカルボニルスルホンアミド、N－（1－メチル）エチルアミノカルボニルスルホンアミド、N－（2－メチル）プロピルアミノカルボニルスルホンアミド、N－（2，2－ジメチル）プロピルアミノカルボニルスルホンアミド、N－ヘキシルアミノカルボニルスルホンアミド、N－シクロヘキシルアミノカルボニルスルホンアミド、N－オクチルアミノカルボニルスルホンアミド、N－デシルアミノカルボニルスルホンアミド、N－ドデシルアミノカルボニルスルホンアミド、N－（1－ピペリジニルカルボニル）スルホンアミド、N－（1－ピペラジニルカルボニル）スルホンアミド、N－（4－モルホリルカルボニル）スルホンアミド等を例示することができる。

【0017】前記一般式（I）で表される芳香族アミド誘導体において、置換基R^1 およびR^2 は、それらが結合している窒素原子と一体になり結合して前記5～7員の飽和複素環構造を形成することができる。

【0018】本発明が提供する前記一般式（I）で表される芳香族アミド誘導体において、Aで示される環は、上記した芳香族炭化水素基または芳香族複素環基であるが、これらの基における置換様式は、R^4 で示される酸性官能基ならびにアミド側鎖が1，2位に置換位置を有するものが好ましく、また、Aが環状アルキル基である場合には、R^4 で示される酸性官能基ならびにアミド側鎖が1，1位に置換されるものが好ましい。

【0019】また、前記一般式（I）で表される芳香族アミド誘導体において、R^3 が置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 アルキル基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_2 ～C_4 アルケニル基、置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_2 ～C_4 アルキニル基、または置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 アルコキシ基である場合には、R^1 が置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 のアルキル基であることが好ましい。

【0020】また、R^3 が無置換のC_5 ～C_{12}アルキル基、無置換のC_5 ～C_{12}アルケニル基、無置換のC_5 ～C_{12}アルキニル基または無置換のC_5 ～C_{12}アルコキシ基である場合には、R^1 が置換もしくは無置換の芳香族炭化水素基または置換もしくは無置換の芳香族複素環基を置換基として有するC_1 ～C_4 のアルキル基であることが好ましい。さらにR^3 が水素原子である場合には、R^1 が置換もしくは無置換の芳香族炭化水素基、置換もしくは無置換の芳香族複素環基、または置換もしくは無置換のC_4 ～C_{12}のアルキル基であることがこのこの好ましい。また、酸性官能基はカルボキシル基または一般式R^5 $CONHSO_2$ －で表される基であることが好ましい。

【0021】本発明の芳香族アミド誘導体としては、例えば以下の化合物を例示することができる。2－（2－（2－ピリジル）アミノベンズアミド）安息香酸；2－（2－（2－チエニル）アミノベンズアミド）安息香酸；2－（2－（2－フルフリル）アミノベンズアミド）安息香酸；2－（2－ブチルアミノベンズアミド）安息香酸；2－（2－オクチルアミノベンズアミド）安息香酸；2－（2－ドデシルアミノベンズアミド）安息香酸；2－（2－シクロヘキルアミノベンズアミド）安息香酸；2－［2－（2－メチルプロピルアミノ）ベンズアミド］安息香酸；2－［2－（1－プロピルブチルアミノ）ベンズアミド］安息香酸；2－［2－（3－メチルブチルアミノ）ベンズアミド］安息香酸；2－［2－（1－メチルヘキシルアミノ）ベンズアミド］安息香酸；2－［2－（2－エチルヘキシルアミノ）ベンズアミド］安息香酸；2－［2－（2，2－ジメチルプロピルアミノ）ベンズアミド］安息香酸；2－［2－（3－フェニルプロピルアミノ）ベンズアミド］安息香酸；2－［2－（6－フェニルヘキシルアミノベンズアミド］安息香酸；2－［2－（N－メチル－N－ヘキシル）アミノベンズアミド］安息香酸；2－（2－イソインドリルベンズアミド）安息香酸；2－（2－ブチルアミノベンズアミド）－4－ニトロ安息香酸；2－（2－ブチルアミノベンズアミド）－5－ニトロ安息香酸；2－（2－ブチルアミノベンズアミド）－5－トリフルオロメチル安息香酸；2－（2－ブチルアミノベンズアミド）－5－ヒドロキシ安息香酸；2－（2－ブチルアミノベンズアミド）－5－メトキシ安息香酸；2－（2－ブチルアミノベンズアミド）－5－クロロ安息香酸；

【0022】2－（2－ブチルアミノ－4－フェネチルベンズアミド）安息香酸；2－（2－フェニルアミノ－4－フェネチルベンズアミド）安息香酸；2－（2－ブチルアミノ－4－ヘキシルベンズアミド）安息香酸；2－（2－ブチルアミノ－4－デシルベンズアミド）安息香酸；2－（2－メチルアミノ－4－フェニルエテニルベンズアミド）安息香酸；2－（2－ブチルアミノ－4

－フェニルエテニルベンズアミド）安息香酸；２－（２－メチルアミノ－４－ベンジルオキシベンズアミド）安息香酸；２－（２－ブチルアミノ－４－ベンジルオキシベンズアミド）安息香酸；２－（２－ブチルアミノ－４－シクロヘキシルオキシベンズアミド）安息香酸；２－（２－ブチルアミノ－４－デシルオキシベンズアミド）安息香酸；２－（２－（２－ピリジル）アミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－（２－チエニル）アミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－（２－フルフリル）アミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－ブチルアミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－メチルアミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－エチルアミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－プロピルアミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－オクチルアミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－デシルアミノ－４－フェニルエチニルベンズアミド）安息香酸；２－（２－ベンジルアミノ－４－フェニルエチニルベンズアミド）安息香酸；２－［２－（３－フェニルプロピル）アミノ－４－フェニルエチニルベンズアミド］安息香酸；

【００２３】２－（２－メチルアミノ－５－フェニルエチニルベンズアミド）安息香酸；２－（２－エチルアミノ－５－フェニルエチニルベンズアミド）安息香酸；２－（２－プロピルアミノ－５－フェニルエチニルベンズアミド）安息香酸；２－（２－ブチルアミノ－５－フェニルエチニルベンズアミド）安息香酸；２－（２－オクチルアミノ－５－フェニルエチニルベンズアミド）安息香酸；２－（２－ベンジルアミノ－５－フェニルエチニルベンズアミド）安息香酸；２－（２－フェニルアミノ－５－フェニルエチニルベンズアミド）安息香酸；２－（２－フェニルアミノ－３－フェニルエチニルベンズアミド）安息香酸；２－［２－（３－フェニルプロピル）アミノ－５－フェニルエチニルベンズアミド］安息香酸；２－［２－（２－ヒドロキシエチル）アミノ－５－フェニルエチニルベンズアミド］安息香酸；２－［２－（２－メルカプトエチル）アミノ－５－フェニルエチニルベンズアミド］安息香酸；２－［２－（２－アミノエチル）アミノ－５－フェニルエチニルベンズアミド］安息香酸；２－［２－［２－（Ｎ，Ｎ－ジメチルアミノ）エチル］アミノ－５－フェニルエチニルベンズアミド］安息香酸；

【００２４】２－（２，６－ジヘキシルアミノベンズアミド）安息香酸；２－（２，６－ジフェニルアミノベンズアミド）安息香酸；５－ヒドロキシ－２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）安息香酸；５－メチル－２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）安息香酸；５－ブロモ－２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）安息香酸；５－メトキシ－２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）安息香酸；５－アミノ－２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）安息香酸；５－メルカプト－２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）安息香酸；３－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）チオフェン－２－カルボン酸

【００２５】５－メチル－２－（２－フェニルアミノ－４－ベンジルオキシベンズアミド）安息香酸；５－ブロモ－２－（２－フェニルアミノ－４－ベンジルオキシベンズアミド）安息香酸；５－メトキシ－２－（２－フェニルアミノ－４－ベンジルオキシベンズアミド）安息香酸；５－アミノ－２－（２－フェニルアミノ－４－ベンジルオキシベンズアミド）安息香酸；５－メルカプト－２－（２－フェニルアミノ－４－ベンジルオキシベンズアミド）安息香酸；３－（２－フェニルアミノ－４－ベンジルオキシベンズアミド）チオフェン－２－カルボン酸２－［４－（１－オクチニル）－２－フェニルアミノベンズアミド］安息香酸；２－［４－（１－ペンチニル）－２－フェニルアミノベンズアミド］安息香酸；２－［４－（３，３－ジメチルブタン－１－イル）－２－フェニルアミノベンズアミド］安息香酸；２－［２－ブチルアミノ－４－（３，３－ジメチルブタン－１－イル）ベンズアミド］安息香酸；２－［４－（３－シクロヘキシルプロパン－１－イル）－２－フェニルアミノベンズアミド］安息香酸；２－［２－ブチルアミノ－４－（３，３－ジメチルブタン－１－イル）ベンズアミド］安息香酸；

【００２６】２－［２－ブチルアミノ－４－（２－フルフリル）エチニルベンズアミド］安息香酸；２－［２－フェニルアミノ－５－（２－ピリジル）エチニルベンズアミド］安息香酸；２－［２－フェニルアミノ－５－（２－チエニル）エチニルベンズアミド］安息香酸；２－［２－ブチルアミノ－５－（３－メトキシプロパン－１－イル）ベンズアミド］安息香酸；２－［２－ブチルアミノ－５－（３，３－ジエトキシプロパン－１－イル）ベンズアミド］安息香酸；２－［２－ブチルアミノ－５－（４－ニトロフェニル）エチニルベンズアミド］安息香酸；２－［２－ブチルアミノ－５－（４－ヒドキシフェニル）エチニルベンズアミド］安息香酸；２－［２－ブチルアミノ－５－（４－シアノフェニル）エチニルベンズアミド］安息香酸；２－［２－ブチルアミノ－５－（４－アミノフェニル）エチニルベンズアミド］安息香酸；

【００２７】４－ベンジルオキシ－２－フェニルアミノ－Ｎ－（２－スルファモイルフェニル）ベンズアミド；２－ブチルアミノ－４－フェニルエチニル－Ｎ－（２－スルファモイルフェニル）ベンズアミド；２－（２－ピ

リジル）アミノ－4－フェニルエチニル－N－（2－スルファモイルフェニル）ベンズアミド；2－ブチルアミノ－4－（3，3－ジメチルブタン－1－イル）－N－（2－スルファモイルフェニル）ベンズアミド；4－（3，3－ジメチルブタン－1－イル）－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド；N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）フェニルスルホニル］アセトアミド；N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）フェニルスルホニル］ブタンアミド；N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）フェニルスルホニル］ピバルアミド；2－メチル－N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）フェニルスルホニル］プロパンアミド；N－［2－（2－ブチルアミノ－4－フェニルエチニルベンズアミド）フェニルスルホニル］アセトアミド；N－［2－（2－ブチルアミノ－4－フェニルエチニルベンズアミド）フェニルスルホニル］ヘキサンアミド

【0028】N－［2－［2－ブチルアミノ－4－（3，3－ジメチルブタン－1－イル）ベンズアミド］フェニルスルホニル］アセトアミド；N－［2－［2－ブチルアミノ－4－（3，3－ジメチルブタン－1－イル）ベンズアミド］フェニルスルホニル］ピバルアミド；N－［2－［4－（3，3－ジメチルブタン－1－イル）－2－フェニルアミノベンズアミド］フェニルスルホニル］アセトアミド；N－［2－［4－（1－オクチニル）－2－フェニルアミノベンズアミド］フェニルスルホニル］アセトアミド；N－［2－［2－ブチルアミノ－4－（1－オクチニル）ベンズアミド］フェニルスルホニル］アセトアミド；N－［2－（2－フェニルアミノ－4－フェニルエテニルベンズアミド）フェニルスルホニル］アセトアミド；N－［2－［4－（3，3－ジメチルブタン－1－エニル）－2－フェニルアミノベンズアミド］フェニルスルホニル］アセトアミド；N－［2－［2－ブチルアミノ－4－（1－オクチニル）ベンズアミド］フェニルスルホニル］アセトアミド；N－［2－［（2－メチル）プロピルオキシカルボニルスルファモイル］フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－［（2，2－ジメチル）エトキシカルボニルスルファモイル］フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－（フェニルオキシカルボニルスルファモイル）フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－（ヘキシルオキシカルボニルスルファモイル）フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；2－ブチルアミノ－N－［［N－（2－メチルプロピル）オキシカルボニルスルファモイル］フェニル］－4－フェニルエチニルベンズアミド；2－ブチルアミノ－N－［2－（フェニルオキシカルボニルスルファモイル）フェニル］－4－フェニルエチニルベンズアミド；

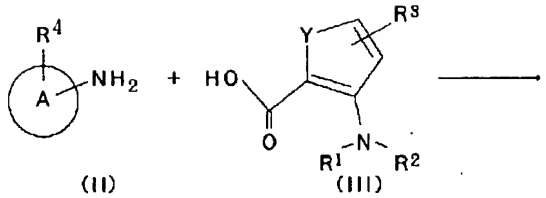
【0029】N－［2－（メチルアミノカルボニルスルファモイル）フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－［（2－メチル）プロピルアミノカルボニルスルファモイル］フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－（フェニルアミノカルボニルスルファモイル）フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－（ブチルアミノカルボニルスルファモイル）フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－（シクロヘキシルアミノカルボニルスルファモイル）フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－［（1－ピペリジノ）カルボニルスルファモイル］フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド；N－［2－［（4－メチルピペラジノ）カルボニルスルファモイル］フェニル］－2－フェニルアミノ－4－フェニルエチニルベンズアミド：

【0030】本発明の芳香族アミド誘導体は、R^4 の酸性官能基が遊離カルボン酸あるいはスルホン酸等の場合にはその酸自体、またはその薬理学的に許容される塩のいずれの形態でも本発明の医薬として使用することができる。そのような塩としては、慣用の無毒性の塩であって、無機塩基との塩、例えばアルカリ金属塩（例えば、ナトリウム塩、カリウム塩など）、アルカリ土類金属塩（例えば、カルシウム塩、マグネシウム塩など）、アンモニウム塩、有機塩基との塩、例えば有機アミン塩（例えば、トリエチルアミン塩、ピリジン塩、ピコリン塩、エタノールアミン塩、トリエタノールアミン塩、N，N－ジメチルアミノエチルアミン塩など）、あるいは塩基性アミノ酸との塩等を挙げることができる。

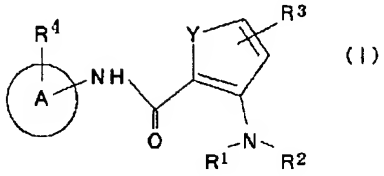
【0031】本発明の芳香族アミド誘導体は、例えば以下の方法に従って製造することができる。かかる製造方法を化学式で示せば以下のとおりにまとめられる。

【0032】

【化3】



(II)　　(III)



(I)

【００３３】式中、R^1，R^2，R^3，R^4，Yおよび環Aは前記定義のとおりである。すなわち、本発明の芳香族アミド誘導体は基本的には、目的とする式（Ｉ）の化合物に対応する式（ＩＩ）で示されるアミノ化合物と、式（ＩＩＩ）で示されるカルボン酸化合物とを縮合することにより製造することができる。

【００３４】本縮合反応は縮合剤の存在下に行うことができ、縮合剤としては、例えばジシクロヘキシルカルボジイミド、１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミドヒドロクロリド等のカルボジイミド試薬、カルボニルジイミダゾール、２－クロロ－１－メチルピリジニウムヨウ化物塩等を用いることができる。

【００３５】あるいは、式（ＩＩＩ）で示されるカルボン酸化合物を、塩化チオニルまたは五塩化リン等のハロゲン化試薬と反応させ、対応する酸ハライドに変換するか、または例えばｐ－トルエンスルホン酸クロリド、クロロ炭酸エチル、ピバロイルクロリド等により反応活性体である酸無水物に変換した後、式（ＩＩ）で示されるアミノ化合物と反応させることにより行うこともできる。

【００３６】また本縮合反応は、不活性な溶媒、例えばジエチルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類；ベンゼン、トルエン、キシレン等の芳香族炭化水素；シクロペンタン、シクロヘキサン等の炭化水素；ジクロルメタン、ジクロルエタン、トリクロロエタン、クロロホルム等のハロゲン化炭化水素；アセトニトリル、プロピオニトリル等のニトリル類；酢酸エチル等のエステル類；Ｎ，Ｎ－ジメチルホルムアミド、ジメチルスルホキシド等から選択される適当な溶媒を用いることができる。

【００３７】さらに、本縮合反応は塩基の存在下に行うことができる。塩基としては、例えば、水素化ナトリウム、水素化カリウム等のアルカリ金属水素化物；水酸化ナトリウム、水酸化カリウム等のアルカリ金属水酸化物；炭酸ナトリウム、炭酸カリウム、炭酸マグネシウム、炭酸カルシウム等のアルカリ金属（または土類金属）炭酸化物；炭酸水素ナトリウム、炭酸水素カリウム等のアルカリ金属炭酸水素化物；ナトリウムメトキシド、ナトリウムエトキシド、カリウムメトキシド、カリウムエトキシド、カリウム第三ブトキシド等のアルカリ金属アルコキシド；トリメチルアミン、トリエチルアミン、Ｎ，Ｎ－ジイソプロピル－Ｎ－エチルアミン等のトリアルキルアミン；ピリジン、ジメチルアミノピリジン、ピコリン、ルチジン等のピリジン化合物等のような有機塩基または無機塩基をあげることができる。その塩基の使用量は、カルボン酸化合物に対して１～１０倍当量使用するのが好ましい。

【００３８】この場合の縮合反応における式（ＩＩ）のアミノ化合物と式（ＩＩＩ）のカルビオン酸のそれぞれの使用量は、ほぼ等モル量で行うことが好ましい。また、反応温度ならびに反応時間は反応させる式（ＩＩ）ならびに（ＩＩＩ）の化合物の種類等により一概に限定されないが、ほぼ０℃ないし使用する溶媒の沸点程度の温度条件下に、０．１ないし２５時間程度反応させることにより収率良く目的とする化合物を得ることができる。また、縮合剤の使用量は、反応させる式（ＩＩ）および（ＩＩＩ）の化合物に対して１～１０倍当量添加させるのが良い。

【００３９】一方、上記の縮合反応により得られた前記一般式（Ｉ）で示される芳香族アミド誘導体において、置換基R^4がカルボン酸エステルである場合には、通常のエステル加水分解反応、例えばメタノール、エタノール、プロパノール等のアルコール系溶媒中、水酸化ナトリウム水溶液、水酸化カリウム水溶液等のアルカリとの反応により、遊離カルボン酸へ誘導することができる。また、前記一般式（Ｉ）で示される芳香族アミド誘導体において、置換基R^4がアシルスルホンアミド基である化合物は、例えば上記縮合反応で得られた式（Ｉ）で示される芳香族アミド誘導体の置換基R^4がスルホンアミド基である化合物を、上記した不活性な溶媒中で上記した適当な塩基の存在下アシルハライドを反応させることにより誘導することもできる。

【００４０】上記したこれらの反応を適宜組み合わせることにより目的とする前記一般式（Ｉ）で示される芳香族アミド誘導体を得ることができ、必要に応じて反応溶液を通常行われている精製手段、例えば沪過、デカンテーション、抽出、洗浄、溶媒留去、カラムまたは薄層クロマトグラフィー、再結晶、蒸留等に付すことにより単離精製することができる。

【００４１】本発明の前記一般式（Ｉ）で示される芳香族アミド誘導体またはその薬理学的に許容される塩を医薬としてヒトに投与する場合、年齢および対象疾患の症状等により異なるが、その有効量、例えば、通常１日に５～３０ｍｇを１～３回に分け、経口投与するのが好ましい。本発明の医薬は、種々の剤型、例えば錠剤、カプセル剤、顆粒剤、散剤、トローチ剤、液剤等の経口投与

製剤とすることができる。これらの製剤化は、それ自体公知の方法によって行い得る。例えば、本発明の式（Ｉ）の化合物をデンプン、マンニトール、乳糖等の賦形剤；カルボキシメチルセルロースナトリウム、ヒドロキシプロピルセルロース等の結合剤；結晶セルロース、カルボキシメチルセルロース等の崩壊剤；タルク、ステアリン酸マグネシウム等の滑沢剤；軽質無水ケイ酸等の流動性向上剤等を適宜組み合わせて処方することにより、錠剤、カプセル剤、顆粒剤、散剤、トローチ剤等を製造することができる。

【００４２】また本発明の医薬は、注射剤とすることもできる。この製剤化は、例えば、界面活性剤や分散剤等によりあらかじめ生理食塩水等の水担体に分散または可溶化しておいてもよいし、あるいはまた、必要時にその都度分散または可溶化し得るように注射用結晶製剤または凍結乾燥製剤としておいてもよい。上記の水担体にはｐＨ調整剤や安定化剤を任意成分として添加してもよい。かかる注射剤の投与量および投与経路は特に限定されず、病状や患者の特性に合わせて、静脈内、動脈内、皮下または腹腔内に安全かつ必要な量を、一気にまたは点滴等により投与することができる。

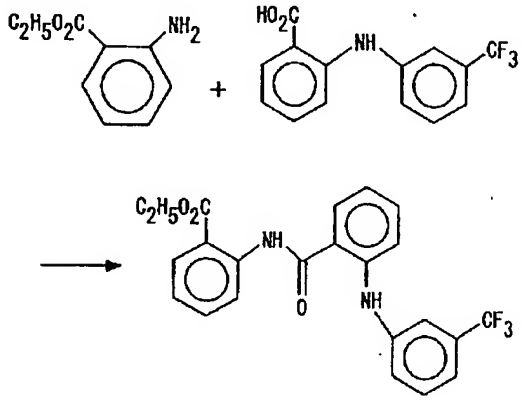
【００４３】

【実施例】以下に本発明を参考例、実施例および薬理試験例によりさらに詳細に説明するが、本発明は以下の記載によって何ら限定されるものではない。

【００４４】参考例１：２－［２－（３－トリフルオロメチルフェニルアミノ）ベンズアミド］安息香酸エチル

【００４５】

【化４】



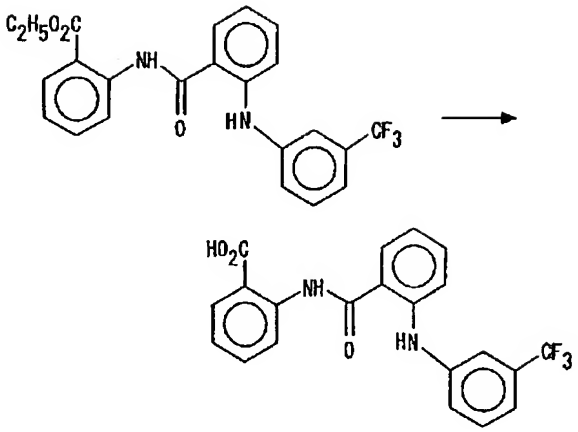
【００４６】２－（３－トリフルオロメチルフェニルアミノ）安息香酸１．５ｇ（５．３３ｍｍｏｌ）の無水ベンゼン溶液（２０ｍｌ）に塩化チオニル２．０ｍｌ、Ｎ，Ｎ－ジメチルホルムアミド数滴を加え、２時間加熱還流した。室温まで冷却後、過剰の塩化チオニルを減圧下留去し、残留物をベンゼン１０ｍｌに溶解し、再度減圧下溶媒を留去した。残留物を酢酸エチル１５ｍｌに溶解し、これを氷冷下炭酸カリウム１．３０ｇ（１０．６７ｍｍｏｌ）、２－アミノ安息香酸エチル０．７８ｍｌ（５．３３ｍｍｏｌ）の水（１５ｍｌ）、酢酸エチル（１０ｍｌ）の混合溶液に滴下し、室温で４時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下濃縮した。残留物をシルカゲルカラムクロマトグラフィーで精製し、標記化合物１．８２ｇ（収率８０．１％）を得た。

【００４７】ＮＭＲ（$CDCl_3$）δ：１．４３（３Ｈ，ｔ，Ｊ＝７Ｈｚ），４．４２（２Ｈ，ｑ，Ｊ＝７Ｈｚ），６．９８（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，６Ｈｚ，２Ｈｚ），７．１４（１Ｈ，ｔ，Ｊ＝８Ｈｚ），７．１９－７．２６（１Ｈ，ｍ），７．３４－７．４４（４Ｈ，ｍ），７．４７（１Ｈ，ｓ），７．６０（１Ｈ，ｄｔ，Ｊ＝８Ｈｚ，１Ｈｚ），７．８４（１Ｈ，ｄ，Ｊ＝８Ｈｚ），８．１１（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），８．７９（１Ｈ，ｄ，Ｊ＝８Ｈｚ），９．７６（１Ｈ，ｓ），１２．００（１Ｈ，ｓ）

【００４８】実施例１：２－［２－（３－トリフルオロメチルフェニルアミノ）ベンズアミド］安息香酸

【００４９】

【化５】



【0050】参考例1で製造した2－［2－（3－トリフルオロメチルフェニルアミノ）ベンズアミド］安息香酸エチル0．66g（1．54mmol）のエタノール溶液（15ml）に1N－水酸化ナトリウム水溶液15mlを加え、2時間加熱還流した。室温まで冷却し、エタノールを減圧下留去し、残留物をエーテルで抽出した。有機層を1N－塩酸、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下濃縮した。残留物をエーテルーヘキサンで再結晶し、標記化合物0．44g（収率71．6%）を得た。

【0051】NMR（$CDCl_3$）δ：6．96（1H，ddd，J＝8Hz，6Hz，2Hz），7．15－7．29（2H，m），7．35－7．45（4H，m），7．48（1H，s），7．68（1H，dt，J＝8Hz，1Hz），7．79（1H，d，J＝8Hz），8．19（1H，d，J＝8Hz），8．83（1H，d，J＝8Hz），9．70（1H，s），11．73（1H，s）

IR（ν，cm^{-1}，KBr）：3500－2600，1708，1652，1612，1582，1456，1336，1210，1112，752，740

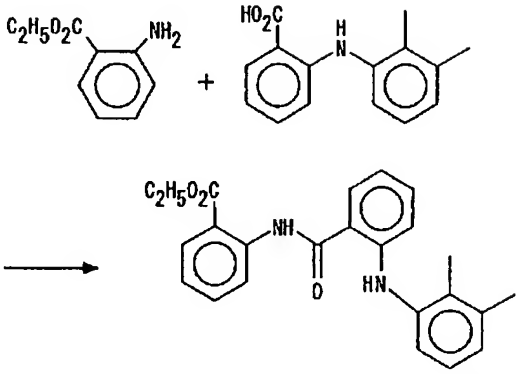
MS（m／z，%）：400（M^+，50），382（6），263（100），264（48）

融点：189～192℃

【0052】参考例2：2－［2－（2，3－ジメチルフェニルアミノ）ベンズアミド］安息香酸エチル

【0053】

【化6】



【0054】2－（2，3－ジメチルフェニルアミノ）安息香酸2．0g（8．29mmol）の無水ベンゼン溶液（20ml）に塩化チオニル2．0ml、N，N－ジメチルホルムアミド数滴を加え、2時間加熱還流した。室温まで冷却後、過剰の塩化チオニルを減圧下留去し、残留物をベンゼン10mlに溶解し、再度減圧下溶媒を留去した。残留物を酢酸エチル10mlに溶解し、これを氷冷下炭酸カリウム2．1g（17．41mmol）、2－アミノ安息香酸エチル1．2ml（8．29mmol）の水（15ml）、酢酸エチル（10ml）の混合溶液に滴下し、室温で3時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下濃縮した。残留物をシリカゲルカラムクロマトグラフィーで精製し、標記化合物1．3g（収率40．4%）を得た。

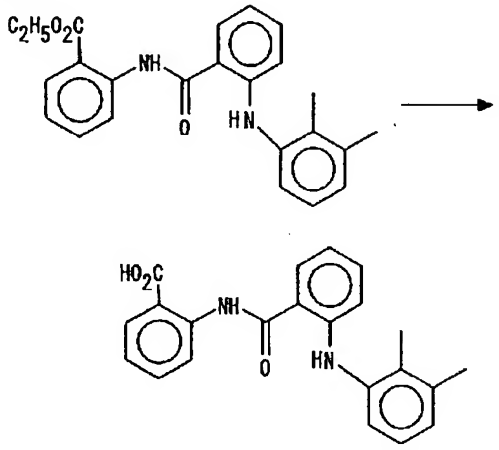
【0055】NMR（$CDCl_3$）δ：1．44（3H，t，J＝7Hz），2．22（3H，s），2．33（3H，s），4．43（2H，q，J＝7Hz），6．81（1H，dt，J＝7Hz，1Hz），6．88（1H，d，J＝8Hz），6．98（1H，d，J＝7Hz），7．04－7．30（4H，m），7．59（1H，dt，J＝8Hz，1Hz），7．82（1H，dd，J＝8Hz，1Hz），8．11（1H，dd，J＝8Hz，1Hz），8．83（1H，d，J＝8Hz），9．48（1H，s），11．96（1H，

s）

【0056】実施例2：2－［2－（2，3－ジメチルフェニルアミノ）ベンズアミド］安息香酸

【0057】

【化7】



【0058】参考例2で製造した2－［2－（2，3－ジメチルフェニルアミノ）ベンズアミド］安息香酸エチル0．61g（1．84mmol）のメタノール溶液（15ml）に1N－水酸化ナトリウム15mlを加え、3時間加熱還流した。室温まで冷却し、メタノールを減圧下留去し、残留物をエーテルで抽出した。有機層を1N－塩酸、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下濃縮した。残留物をエーテル－ヘキサンで再結晶し、標記化合物0．34g（収率60．2%）を得た。

【0059】NMR（$CDCl_3$）δ：2．22（3H，s），2．33（3H，s），6．79（1H，t，J=8Hz），6．89（1H，d，J=8Hz），6．99（1H，d，J=7Hz），7．09（1H，t，J=8Hz），7．13－7．22（2H，m），7．23－7．31（1H，m），7．67（1H，dt，J=8Hz，1Hz），7．76（1H，d，J=7Hz），8．19（1H，dd，J=8Hz，1Hz），8．87（1H，d，J=8Hz），9．43（1H，s），11．69（1H，s）

IR（ν，cm^{-1}，KBr）：3380，3500－2400，1696，1646，1582，1294，1254，1212，754，650

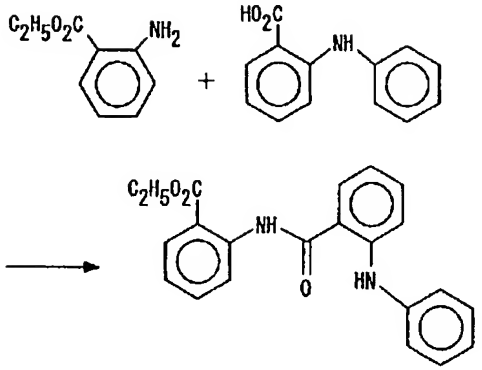
MS（m／z，%）：360（M^+，58），342（8），223（100），224（43）

融点：107～108℃

【0060】参考例3：2－（2－フェニルアミノベンズアミド）安息香酸エチル

【0061】

【化8】



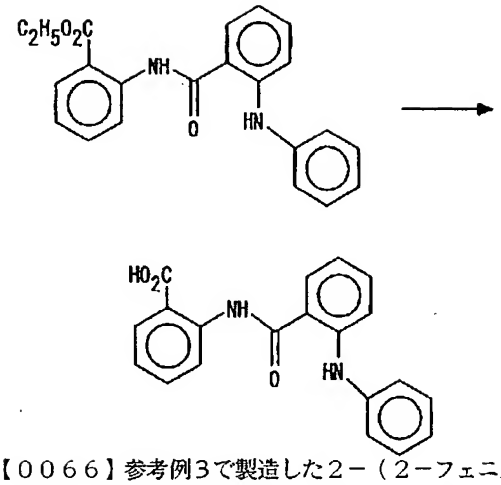
【0062】2－フェニルアミノ安息香酸0．50g（2．34mmol）の無水ベンゼン溶液（10ml）に塩化チオニル1．0ml、N，N－ジメチルホルムアミド数滴を加え、2時間加熱還流し、溶媒を減圧下留去した。残留物をベンゼン10mlに溶解し、再度減圧下溶媒を留去した。残留物を酢酸エチル10mlに溶解し、これを氷冷下炭酸カリウム0．65g（4．69mmol）および2－アミノ安息香酸エチル0．34ml（2．25mmol）の水（15ml）、酢酸エチル（10ml）の混合溶液に滴下し、室温で18時間撹拌した。その後有機層を水、1N－塩酸、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。シリカゲルカラムクロマトグラフィーで精製し、標記化合物0．36g（収率42．2%）を得た。

【0063】NMR（$CDCl_3$）δ：1．43（3H，t，J=7Hz），4．42（2H，q，J=7Hz），6．88（1H，dt，J=7Hz，1Hz），7．03（1H，t，J=7Hz），7．12（1H，t，J=7Hz），7．20－7．43（6H，m），7．59（1H，dt，J=8Hz，1Hz），7．81（1H，d，J=8Hz），8．10（1H，dd，J=8Hz，1Hz），8．80（1H，d，J=8Hz），9．63（1H，s），11．94（1H，s）

【0064】実施例3：2－（2－フェニルアミノベンズアミド）安息香酸

【0065】

【化9】



【0066】参考例3で製造した2－（2－フェニルアミノベンズアミド）安息香酸エチル0．14g（0．337mmol）のメタノール溶液に1N水酸化ナトリウム15mlを加え、2時間加熱還流した。メタノールを減圧下留去し、エーテルで洗浄した。水層に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで2回抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンで再結晶し、標記化合物0．10g（収率74．2%）を得た。

【0067】NMR（DMSO－d_6）δ：6．91－7．04（2H，m），7．15－7．26（3H，m），7．26－7．37（3H，m），7．42（1H，dt，J＝8Hz，1Hz），7．65（1H，dt，J＝8Hz，1Hz），7．78（1H，d，J＝7Hz），8．03（1H，dd，J＝8Hz，1Hz），9．30（1H，s），12．01（1H，s）

IR（ν，cm^{-1}，KBr）：3372，3400－2700，1696，1646，1584，1504，1452，1210，750

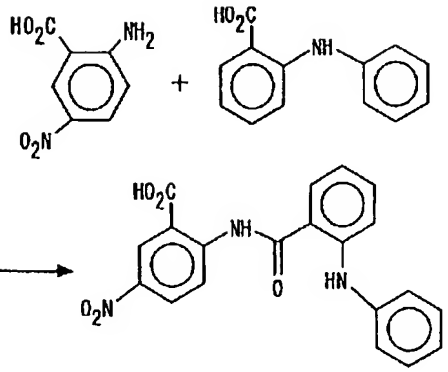
MS（m／z，%）：332（M^+，58），314（5），195（100），223（14），196（50），167（30）

融点：239～240℃

【0068】実施例4：5－ニトロ－2－（2－フェニルアミノベンズアミド）安息香酸

【0069】

【化10】



【0070】2－フェニルアミノ安息香酸0．50g（2．34mmol）の無水ベンゼン溶液（10ml）に塩化チオニル0．26ml（3．51mmol）を加え、2時間室温で撹拌し、減圧下溶媒を留去した。残留物の塩化メチレン溶液（10ml）を氷冷下2－アミノ－5－ニトロ安息香酸427mg（2．34mmol）およびトリエチルアミン0．65ml（4．68mmol）の塩化メチレン溶液（100ml）に滴下し、室温で18時間撹拌した。有機層を水、1N－塩酸、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。シリカゲルカラムクロマトグラフィーで精製し、標記化合物300mg（収率34%）を得た。

【0071】NMR（$CDCl_3$）δ：6．95－7．01（2H，m），7．17（2H，d，J＝7Hz），7．28－7．34（3H，m），7．45（1H，ddd，J＝7Hz，7Hz，1Hz），7．79（1H，d，J＝7Hz），8．49（1H，dd，J＝7Hz，2Hz），7．76（1H，d，J＝7Hz），8．76（1H，d，J＝2Hz），8．86（1H，dd，J＝7Hz，2Hz），9．20（1H，br－s），12．41（1H，br－s）

IR（ν，cm^{-1}，KBr）：1706，1646，1598，1574，1556，1498，1450，1346，1286，1254

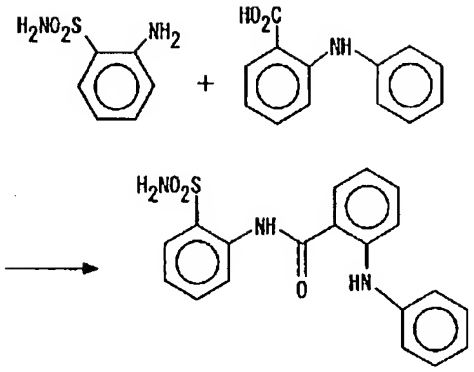
EI－MS（m／z，%）：377（M^+，48），347（11），197（10），196（78），168（8）

融点：232～233℃

【0072】実施例5：2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド

【0073】

【化11】



【0074】2－フェニルアミノ安息香酸1g（4．6mmol）の無水ベンゼン溶液（10ml）に塩化チオニル0．26ml（6．9mmol）を加え、2時間室温で撹拌し、減圧下溶媒を留去した。残留物の塩化メチレン溶液（10ml）を氷冷下2－アミノベンゼンスルホンアミド808mg（4．6mmol）のピリジン溶液（10ml）に滴下し、室温で18時間撹拌し、塩化メチレンを留去した。残留物を酢酸エチルで抽出し水、1N－塩酸、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。シリカゲルカラムクロマトグラフィーで精製し、標記化合物1．2g（収率70％）を得た。

【0075】NMR（$CDCl_3$）δ：4．89（2H，br－S），6．86（1H，ddd，J＝6Hz，6Hz，1Hz），7．06（1H，ddd，J＝6Hz，6Hz，1Hz），7．21－7．30（7H，m），7．63（1H，dd，J＝6Hz，6Hz），7．67（1H，d，J＝6Hz），7．97（1H，d，J＝6Hz），8．40（1H，d，J＝6Hz），9．49（1H，br－S），9．87（1H，br－s）

IR（ν，cm^{-1}，KBr）：1644，1580，1516，1506，1472，1414，1332，1290，1258，1222，1168，1156

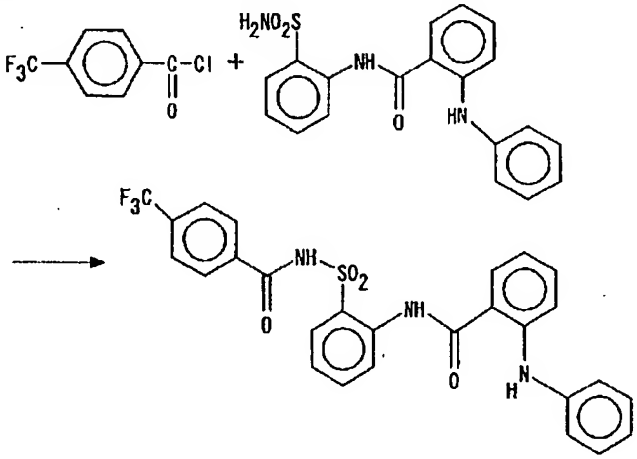
EI－MS（m／z，％）：367（M^+，52），236（17），196（65），195（100），167（37）

融点：126～127℃

【0076】実施例6：N－［2－（4－ベンジルオキシ－2－フェンニルアミノベンズアミド）ベンゼンスルフォニル］ベンズアミド

【0077】

【化12】



【0078】実施例5で製造した4－ベンジルオキシ－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド300mg（0．82mmol）、4－トリフルオロメチルベンゾイルクロリド0．24ml（1．64mmol）および炭酸カリウム340mg（2．4mmol）の水－ジオキサン1：1溶液（10ml）を18時間撹拌した。溶媒を留去し、残留物を水および飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。シリカゲルカラムクロマトグラフィーで精製し、標記化合物200mg（収率45％）を得た。

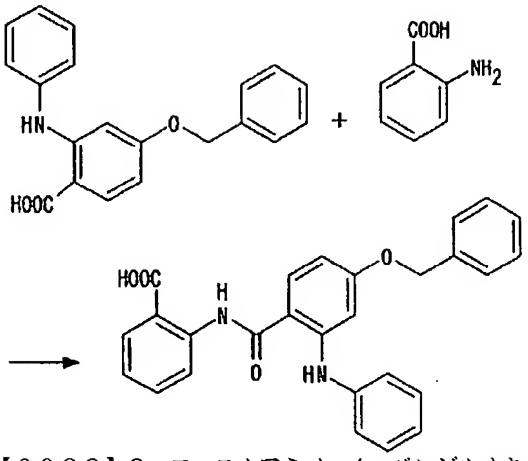
【0079】NMR（$CDCl_3$）δ：6．92（1H，ddd，J＝7Hz，7Hz，1Hz），7．00（1H，ddd，J＝7Hz，7Hz，1Hz），7．17（2H，d，J＝7Hz），7．29－7．45（5H，m），7．64－7．70（3H，m），7．95（1H，dd，J＝7Hz，1Hz），7．96－8．10（3H，m），8．23（1H，d，J＝7Hz），9．40（1H，br－S），10．65（1H，br－s）

IR（ν，cm^{-1}，KBr）：1696，1662，1644，1580，1518，1474，1452，1324，1288

EI－MS（m／z，％）：539（M^+，25），288（6），197（7），196（57），195（100），173（9），169（8）

【0080】実施例7：2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）安息香酸

【0081】
【化13】

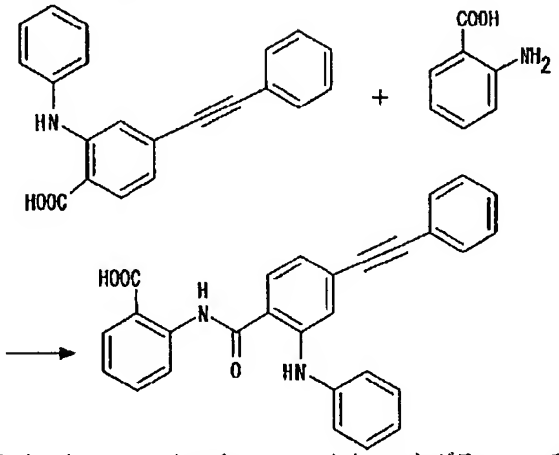


【0082】2－フェニルアミノ－4－ベンジルオキシ安息香酸100mg（0．31mmol）の塩化メチレン（10ml）溶液に窒素雰囲気下、塩化チオニル0．04ml（0．50mmol）を加え室温で1時間撹拌した後、溶媒を減圧下留去した。残留物を塩化メチレン10mlに溶解し、これを氷冷下トリエチルアミン0．2ml（1．30mmol）、2－アミノ安息香酸0．04g（0．31mmol）の塩化メチレン（10ml）溶液に滴下し、室温で18時間撹拌した。1N－塩酸を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製し標記化合物38mg（収率27．7％）を得た。

【0083】NMR（$CDCl_3$）δ：5．04（2H，s），6．49（1H，dd，J＝9Hz，2Hz），6．86（1H，d，J＝2Hz），7．05（1H，t，J＝7Hz），7．11－7．18（3H，m），7．25－7．42（7H，m），7．64（1H，dt，J＝8Hz，1Hz），7．73（1H，d，J＝9．0Hz），8．15（1H，dd，J＝8Hz，1Hz），8．81（1H，d，J＝8Hz），9．93（1H，s），11．64（1H，s）
IR（ν，cm^{-1}，KBr）：3500－2500，1682，1652，1580，1524，1452，1254，752
EI－MS（m／z，％）：438（M^+，20），420（43），302（11），301（16），211（9），91（100）
融点：203～204℃

【0084】実施例8：2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0085】
【化14】



【0086】2－フェニルアミノ－4－フェニルエチニル安息香酸200mg（0．64mmol）の塩化メチレン（10ml）溶液に窒素雰囲気下、塩化チオニル0．15ml（1．90mmol）を加え、室温で1時間撹拌した後、溶媒を減圧下留去した。残留物を塩化メチレン10mlに溶解し、これを氷冷下トリエチルアミン0．36ml（2．55mmol）、2－アミノ安息香酸0．09g（0．64mmol）の塩化メチレン（10ml）溶液に滴下し、室温で18時間撹拌した。1N－塩酸を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製した後、アセトニトリルで再結晶し、標記化合物37mg（収率13．4％）を得た。

【0087】NMR（DMSO－d_6）δ：7．06（1H，t，J＝7Hz），7．11（1H，dd，J＝8Hz，1Hz），7．19－7．27（3H，m），7．32－7．46（6H，m），7．54－7．60（2H，m），7．65（1H，dt，J＝8Hz，1Hz），7．82（1H，d，J＝8Hz），8．03（1H，dd，J＝8Hz，1Hz），8．57（1H，d，J＝8Hz），9．36（1H，s），12．08（1H，s）

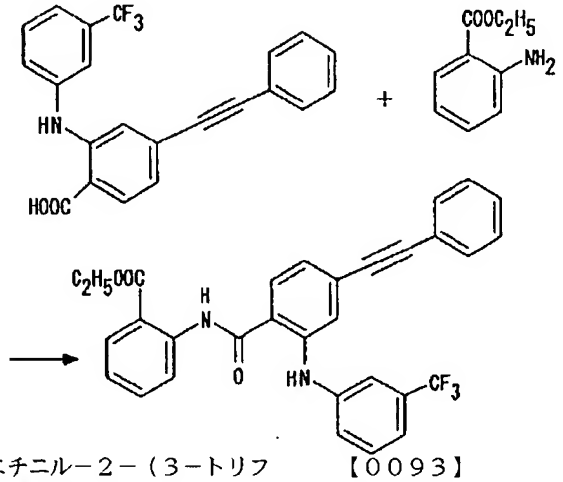
IR（ν，cm^{-1}，KBr）：3324，3400－2300，1682，1650，1582，1556，1416，1266，756
EI－MS（m／z，%）：432（M^+，23），414（100），295（55），188（65），187（58）

融点：220～223℃

【0088】参考例4：2－「4－フェニルエチニル－2－（3－トリフルオロメチルフェニルアミノ）ベンズアミド］安息香酸エチル

【0089】

【化15】



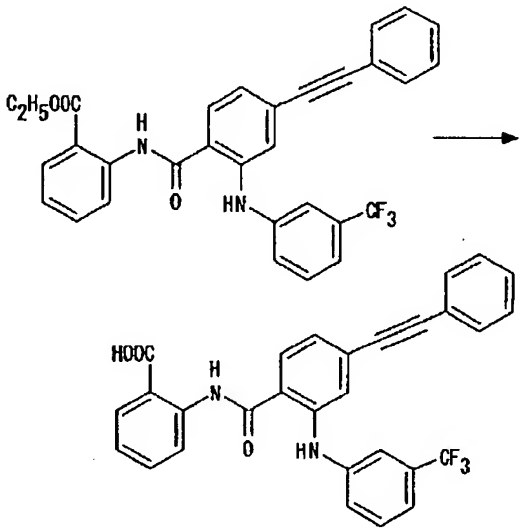
【0090】4－フェニルエチニル－2－（3－トリフルオロフェニルアミノ）安息香酸250mg（0．66mmol）の無水ベンゼン溶液（10ml）に塩化チオニル1．0ml、N，N－ジメチルホルムアミド数滴を加え、2時間加熱還流した。室温まで冷却後、過剰の塩化チオニルを減圧下留去した。残留物をベンゼン10ml に溶解し、再度減圧下溶媒を留去した。残留物を酢酸エチル10mlに溶解し、これに氷冷下炭酸カリウム0．18g（1．31mmol）、2－アミノ安息香酸エチル0．1ml（0．66mmol）の水（15ml）－酢酸エチル（10ml）の混合溶液に滴下し、室温で20時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水、1N－塩酸、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を留去した。シリカゲルカラムクロマトグラフィーで精製し、標記化合物0．10g（収率29．4%）を得た。

【0091】NMR（DMSO－d_6）δ：1．44（3H，t，J＝7Hz），4．43（2H，q，J＝7Hz），7．10（1H，dd，J＝8Hz，1Hz），7．15（1H，ddd，J＝8Hz，7Hz，1Hz），7．27－7．30（1H，m），7．33－7．37（3H，m），7．42－7．54（6H，m），7．61（1H，ddd，J＝8Hz，7Hz，1Hz），7．81（1H，d，J＝8Hz），8．12（1H，dd，J＝8Hz，1Hz），8．78（1H，dd，J＝8Hz，1Hz），9．83（1H，s），12．05（1H，s）

【0092】実施例9：2－［4－フェニルエチニル－2－（3－トリフルオロメチルフェニルアミノ）ベンズアミド］安息香酸

【0093】

【化16】



【0094】参考例4で製造した2－［4－フェニルエチニル－2－（3－トリフルオロメチルフェニルアミノ）ベンズアミド］安息香酸エチル100mg（0．15mmol）のエタノール（10ml）溶液に1N－水酸化ナトリウム水溶液10mlを加え、2時間加熱還流した。エタノールを減圧下留去し、残留物を濃塩酸にて中和し、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルにて再結晶を行い、標記化合物75mg（収率77．6%）を得た。

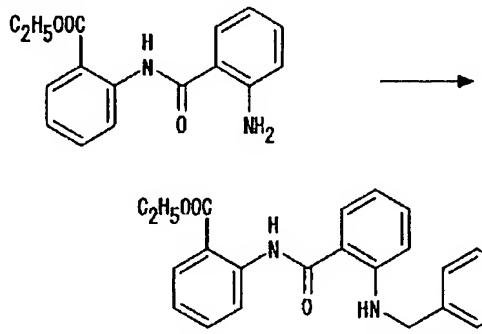
【0095】NMR（DMSO－d_6）δ：7．17－7．28（3H，m），7．38－7．54（7H，m），7．54－7．65（3H，m），7．82（1

H，d，J＝8Hz），8．01（1H，dd，J＝8．Hz，1Hz），8．55（1H，d，J＝8Hz），9．28（1H，s），12．06（1H，s）
IR（ν，cm^{-1}，KBr）：3304，3500－2400，1654，1608，1538，1418，1334，1256，1226，1128，754
EI－MS（m／z，%）：484（M^+，12），483（34），482（100），464（12），363（12），256（27），213（13）
融点：228～230℃

【0096】参考例5：2－（2－ベンジルアミノベンズアミド）安息香酸エチル

【0097】

【化17】



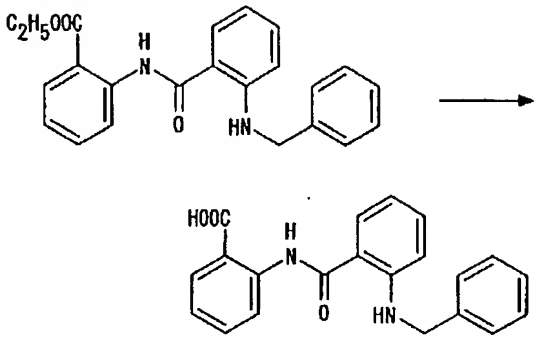
【0098】2－アミノベンズアミド安息香酸エチル1．5g（5．28mmol）のN，N－ジメチルホルムアミド溶液（20ml）に炭酸カリウム0．76g（5．54mmol）およびベンジルブロミド0．6ml（5．54mmol）を加え、室温で18時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムにて乾燥し、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製し、標記化合物968mg（収率49．0%）を得た。

【0099】NMR（$CDCl_3$）δ：1．43（3H，t，J＝7Hz），4．41（2H，q，J＝7Hz），4．46（2H，d，J＝6Hz），6．67（1H，d，J＝8Hz），6．92（1H，dt，J＝7Hz，1Hz），7．10（1H，dt，J＝7Hz，1Hz），7．22－7．41（6H，m），7．57（1H，dt，J＝8Hz，1Hz），7．78（1H，dd，J＝8Hz，1Hz），8．09（1H，dd，J＝8Hz，1Hz），8．30－8．43（1H，m），8．78（1H，dd，J＝8Hz，1Hz），11．88（1H，s）

【0100】実施例10：2－（2－ベンジルアミノベンズアミド）安息香酸

【0101】

【化18】



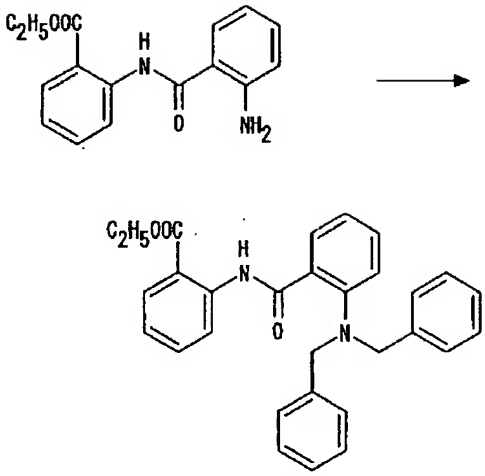
【0102】参考例5で製造した2－（2－ベンジルアミノベンズアミド）安息香酸エチル400mg（1．07mmol）エタノール溶液（15ml）に1N－水酸化ナトリウム水溶液15mlを加え、3時間加熱還流した。エタノールを減圧下留去し、残留物を濃塩酸にて酸性にし酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を留去した。残留物をエーテル／ヘキサンにて再結晶を行い、標記化合物273mg（収率73．7%）を得た。

【0103】NMR（$CDCl_3$）δ：4．47（2H，s），6．66－6．72（2H，m），7．14（1H，dt，J＝8Hz，1Hz），7．22－7．41（7H，m），7．64（1H，dt，J＝8Hz，1Hz），7．73（1H，dd，J＝8Hz，1Hz），8．16（1H，dd，J＝8Hz，1Hz），8．81（1H，dd，J＝8Hz，1Hz），11．63（1H，s）
IR（ν，cm^{-1}，KBr）：3404，3500－2800，1698，1644，1610，1516，1452，1362，1212，756
EI－MS（m／z，%）：346（M^+，80），328（19），210（79），209（80），181（80），180（90），91（100）
融点：175～176℃

【0104】参考例6：2－（2－ジベンジルアミノベンズアミド）安息香酸エチル

【0105】

【化19】



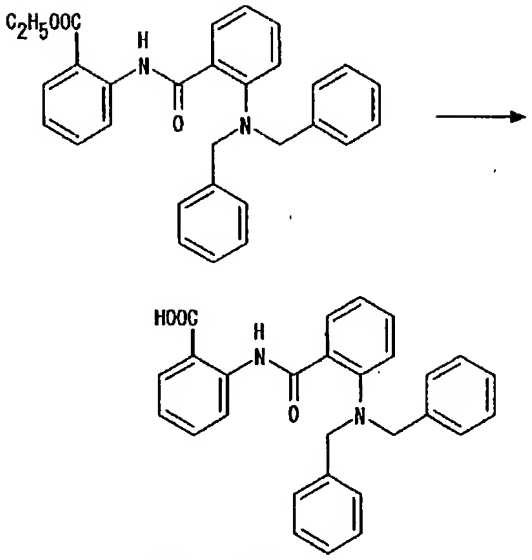
【0106】2－アミノベンズアミド安息香酸エチル1．5g（5．28mmol）のN，N－ジメチルホルムアミド溶液（20ml）に炭酸カリウム1．52g（11．08mmol）およびベンジルブロミド1．3ml（11．08mmol）を加え、室温で18時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムにて乾燥し、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製し、標記化合物1．08mg（収率44．0%）を得た。

【0107】NMR（$CDCl_3$）δ：1．33（3H，t，J＝7Hz），4．28（2H，q，J＝7Hz），4．29（4H，s），6．87（1H，dd，J＝8Hz，1Hz），7．06（1H，dt，J＝8Hz，1Hz），7．11－1．21（11H，m），7．58（1H，dd，J＝8Hz，1Hz），7．74（1H，dd，J＝8Hz，1Hz），8．07（1H，dd，J＝8Hz，1Hz），8．82（1H，dd，J＝8Hz，1Hz），11．88（1H，s）

【0108】実施例11：2－（2－ジベンジルアミノベンズアミド）安息香酸

【0109】

【化20】



【0110】参考例6で製造した2－（2－ジベンジルアミノベンズアミド）安息香酸エチル750mg（1．61mmol）エタノール溶液（10ml）に1N－水酸化ナトリウム水溶液10mlを加え、3時間加熱還流した。エタノールを減圧下留去し、残留物を濃塩酸にて酸性にし酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧留去した。残留物を酢酸エチル／ヘキサンにて再結晶を行い、標記化合物590mg（収率84．0%）を得た。

【0111】NMR（$CDCl_3$）δ：4．27（4H，s），6．86（1H，dd，J＝8Hz，1Hz），7．07（1H，dt，J＝8Hz，1Hz），7．11－7．22（10H，m），7．63（1H，ddd，J＝8Hz，7Hz，1Hz），7．80（1H，dd，J＝8Hz，1Hz），8．06（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．08（1H，s）

IR（ν，cm^{-1}，KBr）：3500－2700，1718，1636，1506，1452，1288，1180，1164，762，698

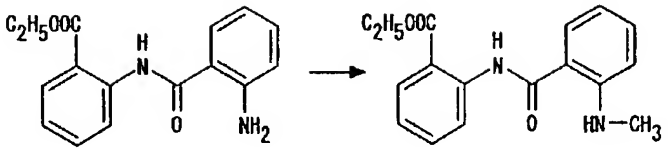
EI－MS（m／z，%）：436（M^+，1），435（4），346（24），345（86），327（18），209（37），208（100），91（80）

融点：147～148℃

【0112】参考例7：2－（メチルアミノベンズアミド）安息香酸エチル

【0113】

【化21】



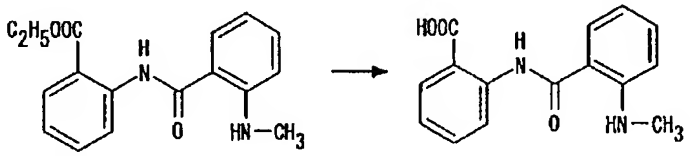
【0114】2－アミノベンズアミド安息香酸エチル1.0g（3.52mmol）のN，N－ジメチルホルムアミド溶液（10ml）に炭酸カリウム0.5g（3.70mmol）およびヨードメタン0.3ml（3.70mmol）を加え、室温で16時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムにて乾燥し、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製し、標記化合物310mg（収率29.5%）を得た。

【0115】NMR（$CDCl_3$）δ：1.42（3H，t，J＝7Hz），2.91（3H，d，J＝5Hz），4.41（2H，q，J＝7Hz），6.69－6.74（2H，m），7.09（1H，dt，J＝8Hz，1Hz），7.38（1H，dt，J＝8Hz，1Hz），7.57（1H，dt，J＝8Hz，1Hz），7.75（1H，dd，J＝8Hz，1Hz），7.82（1H，s），8.09（1H，dd，J＝8Hz，1Hz），8.78（1H，dd，J＝8Hz，1Hz），11.84（1H，s）

【0116】実施例12：2－（2－メチルアミノベンズアミド）安息香酸

【0117】

【化22】



【0118】参考例7で製造した2－（2－メチルアミノベンズアミド）安息香酸エチル95mg（0.32mmol）エタノール溶液（6ml）に1N－水酸化ナトリウム水溶液6mlを加え、1時間加熱還流した。エタノールを減圧下留去し、残留物を濃塩酸にて酸性にし酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧留去した。残留物をエーテル／ヘキサンにて再結晶を行い標記化合物80mg（収率93.1%）を得た。

【0119】NMR（$CDCl_3$）δ：2.83（3H，s），6.67（1H，dt，J＝8Hz，1Hz），7.18（1H，dt，J＝8Hz，1Hz），7.40（1H，dt，J＝8Hz，1Hz），7.60－7.70（3H，m），8.04（1H，dd，J＝8Hz，1Hz），8.62（1H，dd，J＝8Hz，1Hz），11.96（1H，s），13.71（1H，br－s）

IR（ν，cm^{-1}，KBr）：3424，3400－2500，1690，1642，1608，1522，1452，1296，1214，752

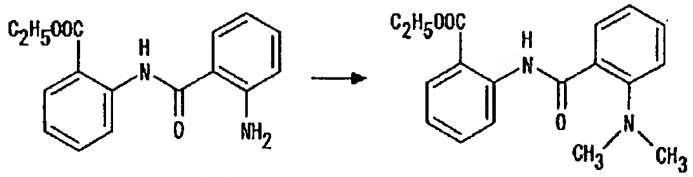
EI－MS（m／z，%）：270（M^+，60），252（6），134（100），105（16），91（30），77（33）

融点：205～207℃

【0120】参考例8：2－（ジメチルアミノベンズアミド）安息香酸エチル

【0121】

【化23】

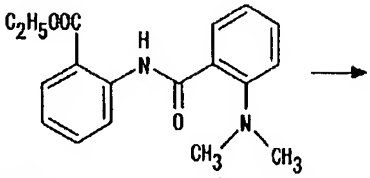


【0122】2－アミノベンズアミド安息香酸エチル1.0g（3.52mmol）のN，N－ジメチルホルムアミド溶液（10ml）に炭酸カリウム1.0g（7.04mmol）およびヨードメタン0.6ml（7.04mmol）を加え、室温で16時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムにて乾燥し、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製し、標記化合物710mg（収率64.6%）を得た。

【0123】NMR（$CDCl_3$）δ：1.39（3H，t，J＝7Hz），2.82（6H，s），4.35（2H，q，J＝7Hz），7.06－7.12（2H，m），7.15（1H，dd，J＝8Hz，1Hz），7.42（1H，ddd，J＝8Hz，7Hz，1Hz），7.56（1H，dd，J＝8Hz，1Hz），7.96（1H，dd，J＝8Hz，1Hz），8.02（1H，dd，J＝8Hz，1Hz），8.9

3（1H，dd，J＝8Hz，1Hz），12．60（1H，s）

【0124】実施例13：2－（2－ジメチルアミノベ



【0126】参考例8で製造した2－（2－ジメチルアミノベンズアミド）安息香酸エチル484mg（1．55mmol）エタノール溶液（10ml）に1N－水酸化ナトリウム水溶液10mlを加え、2時間加熱還流した。エタノールを減圧下留去し、残留物を濃塩酸にて酸性にし酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧留去した。残留物をエーテル／ヘキサンにて再結晶を行い、標記化合物337mg（収率76．5%）を得た。

【0127】NMR（$CDCl_3$）δ：4．27（4H，s），7．09－7．18（3H，m），7．44（1H，ddd，J＝8Hz，7Hz，1Hz），7．64（1H，dt，J＝8Hz，1Hz），7．99（1H，dd，J＝7Hz，1Hz），8．10（1H，dd，J＝8Hz，1Hz），8．97（1H，dd，J＝8Hz，1Hz）

IR（ν，cm^{-1}，KBr）：3400－2400，1716，1636，1580，1512，1450，1378，1208，770，758

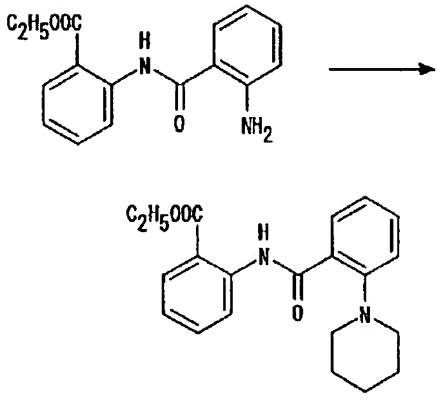
EI－MS（m／z，%）：284（M^+，15），270（3），148（100），147（88），105（16），91（24），77（19）

融点：137～138℃

【0128】参考例9：2－（2－ピペリジルベンズアミド）安息香酸エチル

【0129】

【化25】



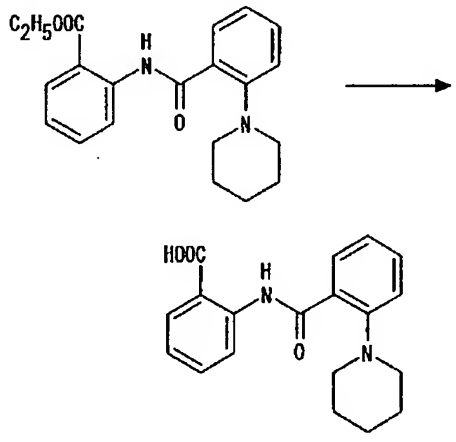
【0130】2－アミノベンズアミド安息香酸エチル500mg（1．76mmol）のN，N－ジメチルホルムアミド溶液（15ml）に炭酸カリウム510mg（3．69mmol）および1，5－ジヨードペンタン0．3ml（2．11mmol）を加え、60℃で20時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、無水硫酸ナトリウムにて乾燥し、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製し、標記化合物75mg（収率12．1%）を得た。

【0131】NMR（$CDCl_3$）δ：1．36（3H，t，J＝7Hz），1．42－1．50（2H，m），1．56－1．67（4H，m），3．03（4H，t，J＝5Hz），4．32（2H，q，J＝7Hz），7．05－7．14（3H，m），7．41（1H，ddd，J＝8Hz，7Hz，1Hz），7．57（1H，dt，J＝8Hz，1Hz），7．86（1H，dd，J＝8Hz，1Hz），8．06（1H，dd，J＝8Hz，1Hz），8．84（1H，d，J＝8Hz），12．29（1H，s）

【0132】実施例14：2－（2－ピペリジルベンズアミド）安息香酸

【0133】

【化26】



【0134】参考例9で製造した2－（2－ピペリジルベンズアミド）安息香酸エチル75mg（0．21mmol）エタノール溶液（10ml）に1N－水酸化ナトリウム水溶液10mlを加え、2時間加熱還流した。エタノールを減圧下留去し、残留物を濃塩酸にて酸性にし酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧留去

した。残留物を酢酸エチル／ヘキサンにて再結晶を行い、標記化合物57mg（収率76．5%）を得た。
【0135】NMR（$CDCl_3$）δ：1．43－1．50（2H，m），1．50－1．65（4H，m），2．88－3．08（4H，m），7．08－7．20（3H，m），7．44（1H，dt，J＝8Hz，1Hz），7．61（1H，dt，J＝8Hz，1Hz），7．91（1H，dd，J＝8Hz，1Hz），8．83（1H，d，J＝8Hz）
IR（ν，cm^{-1}，KBr）：3400－2100，1676，1576，1520，1452，1418，1270，908，766，756
EI－MS（m／z，%）：324（M^+，15），188（90），187（100），159（36）
融点：192～193℃
【0136】参考例10：2－（2－クロロ－4－フェニルエチニルベンズアミド）安息香酸エチル
【0137】
【化27】2－クロロ－4－フェニルエチニル安息香酸0．82g（3．19mmol）の無水ベンゼン溶液（10ml）に塩化チオニル1．0ml及びN，N－ジメチルホルムアミド数滴を加え、1時間加熱還流した後、溶媒を減圧下留去した。残留物を酢酸エチル10ml1に溶解し、これを氷冷下炭酸カリウム0．88g（6．39mmol）及び2－アミノ安息香酸エチル0．47ml（3．19mmol）の水（15ml）及び酢酸エチル（5ml）の混合溶液に滴下し、室温で3時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、酢酸エチル－ヘキサンで再結晶し標記化合物1．08g（収率83．8%）を得た。
【0138】NMR（$CDCl_3$）δ：1．40（3H，t，J＝7Hz），4．37（2H，q，J＝7Hz），7．16（1H，ddd，J＝8Hz，8Hz，1Hz），7．35－7．41（3H，m），7．39－7．58（3H，m），7．59－7．66（3H，m），8．10（1H，dd，J＝8Hz，1Hz），8．89（1H，d，J＝8Hz），11．62（1H，s）
【0139】参考例11：2－（2－クロロ－4－フェニルエチニルベンズアミド）安息香酸
【0140】
【化28】参考例10で製造した（2－クロロ－4－フェニルエチニルベンズアミド）安息香酸エチル1．03g（2．55mmol）のエタノール（20ml）溶液に1M－水酸化ナトリウム水溶液20mlを加え、1時間加熱撹拌した後、エタノールを減圧下留去した。残留物に濃塩酸を加え酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をエタノールで再結晶し、標記化合物0．82g（収率86．0%）を得た。
【0141】NMR（DMSO－d_6）δ：7．26（1H，ddd，J＝8Hz，8Hz，1Hz），7．45－7．50（3H，m），7．59－7．65（2H，m），7．66－7．72（2H，m），7．77（1H，d，J＝8Hz），7．83（1H，d，J＝1Hz），8．04（1H，dd，J＝8Hz，1Hz），8．57（1H，d，J＝8Hz），11．67（1H，s）
【0142】実施例15：2－（2－ヘキシルアミノ－4－フェニルエチニルベンズアミド）安息香酸
【0143】
【化29】参考例10で製造した2－（2－クロロ－4－フェニルエチニルベンズアミド）安息香酸300mg（0．80mmol）のヘキシルアミン（5ml）溶液に炭酸カリウム140mg（0．96mmol）及び5wt．%の活性化銅を加え、封管中170℃で3時間加熱撹拌した後、室温まで冷却し、ヘキシルアミンを減圧下留去した。残留物に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エタノールで再結晶し標記化合物0．12g（収率33．0%）を得た。
【0144】NMR（$CDCl_3$）δ：0．91（3H，t，J＝7Hz），1．28－1．40（4H，m），1．40－1．50（2H，m），1．68－1．76（2H，m），3．20（2H，t，J＝7Hz），6．83（1H，dd，J＝8Hz，1Hz），6．89（1H，d，J＝1Hz），7．14（1H，ddd，J＝8Hz，8Hz，1Hz），7．34－7．39（3H，m），7．54－7．60（2H，m），7．60－7．69（2H，m），8．16（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．64（1H，s）
IR（ν，cm^{-1}，KBr）：3344，2932，1652，1604，1532，1252，762，754
EI－MS（m／z，%）：440（m+，100），422（19），369（29），304（34），232（96）
融点：211－213℃
【0145】実施例16：2－（2－ベンジルアミノ－4－フェニルエチニルベンズアミド）安息香酸
【0146】
【化30】参考例10で製造した2－（2－クロロ－4

－フェニルエチニルベンズアミド）安息香酸260mg（0．70mmol）のベンジルアミン（3ml）溶液に炭酸カリウム0．12g（0．84mmol）及び5wt．%の活性化銅を加え、170℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エタノールで再結晶し標記化合物90mg（収率28．7%）を得た。

【0147】NMR（$CDCl_3$）δ：4．74（2H，s），6．85－6．90（2H，m），7．12－7．17（1H，m），7．26－7．30（1H，m），7．32－7．42（6H，m），7．50－7．55（2H，m），7．64（1H，ddd，J＝8Hz，7Hz，1Hz），7．71（1H，d，J＝8Hz），8．16（1H，dd，J＝8Hz，1Hz），8．79（1H，dd，J＝8Hz，1Hz），11．71（1H，s）

IR（ν，cm^{-1}，KBr）：3240，1682，1650，1604，1538，1266，766，756

EI－MS（m／z，%）：446（m+，100），428（37），310（84），280（87），221（42），193（69），91（22）

融点：226－228℃

【0148】参考例12：2－（2－メチルプロピル）アミノ安息香酸

【0149】

【化31】2－クロロ安息香酸1．0g（6．39mmol）の2－メチルプロピルアミン（3ml）溶液に炭酸カリウム1．06g（7．16mmol）及び5wt．%の活性化銅を加え、封管中170℃で1時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し標記化合物0．99g（収率88．0%）を得た。

【0150】NMR（$CDCl_3$）δ：1．03（6H，d，J＝7Hz），1．99（1H，sept．，J＝7Hz），3．04（2H，d，J＝7Hz），6．56（1H，ddd，J＝8Hz，8Hz，1Hz），6．68（1H，dd，J＝8Hz，1Hz），7．38（1H，ddd，J＝8Hz，7Hz，1Hz），7．98（1H，dd，J＝8Hz，1Hz）

【0151】実施例17：2－［2－（2－メチルプロピルアミノ）ベンズアミド］安息香酸

【0152】

【化32】参考例12で製造した2－（2－メチルプロピル）アミノ安息香酸0．30g（1．55mmol）の無水ベンゼン溶液（5ml）に塩化チオニル0．5ml及びN，N－ジメチルホルムアミド数滴を加え、1時間加熱還流した後、溶媒を減圧下留去した。残留物を塩化メチレン10mlに溶解し、これを、窒素雰囲気下トリエチルアミン0．64ml（4．66mmol）及び2－アミノ安息香酸0．21g（1．55mmol）の塩化メチレン（10ml）溶液に、氷冷下滴下し、室温で18時間撹拌した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エタノールで再結晶し標記化合物0．23g（収率46．9%）を得た。

【0153】NMR（$CDCl_3$）δ：1．06（6H，d，J＝7Hz），2．02（1H，sept，J＝7Hz），3．05（2H，d，J＝7Hz），6．69（1H，dt，J＝8Hz，1Hz），6．76（1H，d，J＝8Hz），7．16（1H，ddd，J＝8Hz，8Hz，1Hz），7．38（1H，ddd，J＝8Hz，7Hz，1Hz），7．67（1H，ddd，J＝8Hz，7Hz，1Hz），7．72（1H，dd，J＝8Hz，1Hz），8．19（1H，dd，J＝8Hz，1Hz），8．84（1H，dd，J＝8Hz，1Hz），11．57（1H，s）

IR（ν，cm^{-1}，KBr）：2962，1658，1602，1576，1532，1256，752，738

EI－MS（m／z，%）：312（m+，41），269（61），251（16），132（100），120（30）

融点：159－160℃

【0154】参考例13：2－シクロヘキシルアミノ安息香酸

【0155】

【化33】2－クロロ安息香酸1．0g（6．39mmol）のシクロヘキシルアミン（3ml）溶液に炭酸カリウム1．06g（7．16mmol）及び5wt．%の活性化銅を加え、封管中170℃で0．5時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し標記化合物1．27g（収率90．6%）を得た。

【0156】NMR（$CDCl_3$）δ：1．34－1．47（5H，m），1．60－1．68（1H，m），1．74－1．83（2H，m），1．98－2．10（2H，m），3．36－3．46（1H，m），6．56（1H，ddd，J＝8Hz，7Hz，1Hz），

６．７１（１Ｈ，ｄ，Ｊ＝８Ｈｚ），７．３６（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，７Ｈｚ，１Ｈｚ），７．９６（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ）

【０１５７】実施例１８：２－［２－（シクロヘキシルアミノ）ベンズアミド］安息香酸

【０１５８】

【化３４】参考例１３で製造した２－シクロヘキシルアミノ安息香酸０．３０ｇ（１．５５ｍｍｏｌ）の無水ベンゼン溶液（１０ｍｌ）に塩化チオニル０．５ｍｌ及びＮ，Ｎ－ジメチルホルムアミド数滴を加え、１時間加熱還流した後、溶媒を減圧下留去した。残留物を塩化メチレン１０ｍｌに溶解し、これを窒素雰囲気下、トリエチルアミン０．５７ｍｌ（４．１１ｍｍｏｌ）及び２－アミノ安息香酸０．１９ｇ（１．３７ｍｍｏｌ）の塩化メチレン（１０ｍｌ）溶液に氷冷下滴下し、室温で１８時間撹拌した。反応溶液に１Ｍ－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エタノールで再結晶し標記化合物０．３０ｇ（収率５９．３％）を得た。

【０１５９】ＮＭＲ（$CDCl_3$）δ：１．２６－１．４０（３Ｈ，ｍ），１．４０－１．５２（２Ｈ，ｍ），１．５８－１．６８（１Ｈ，ｍ），１．７２－１．８４（２Ｈ，ｍ），１．９９－２．０５（２Ｈ，ｍ），３．４４－３．５４（１Ｈ，ｍ），６．６３（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，８Ｈｚ，１Ｈｚ），６．８５（１Ｈ，ｄ，Ｊ＝８Ｈｚ），７．１９（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，８Ｈｚ，１Ｈｚ），７．３４（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，８Ｈｚ，１Ｈｚ），７．６７（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），７．７４（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），８．８６（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），１２．０７（１Ｈ，ｓ）

ＩＲ（ν，cm^{-1}，ＫＢｒ）：２９３６，１６５８，１５７４，１５３２，１２５２，７５４，７４０

ＥＩ－ＭＳ（ｍ／ｚ，％）：３３８（ｍ＋，１００），３２６（５），２９５（２２），２０２（１８），２０１（１６），１５８（４１），１３２（１９），１２０（１９）

融点：２３０－２３２℃

【０１６０】参考例１４：２－（２－クロロベンズアミド）安息香酸エチル

【０１６１】

【化３５】２－クロロ安息香酸３．０ｇ（１９．２ｍｍｏｌ）の無水ベンゼン溶液（３０ｍｌ）に塩化チオニル２．０ｍｌ及びＮ，Ｎ－ジメチルホルムアミド数滴を加え、１時間加熱還流した後、溶媒を減圧下留去した。残留物を酢酸エチル（２０ｍｌ）に溶解し、これを氷冷下炭酸カリウム５．３ｇ（３８．３ｍｍｏｌ）及び２－アミノ安息香酸エチル２．８ｍｌ（１９．２ｍｍｏｌ）の水（３０ｍｌ）及び酢酸エチル（１５ｍｌ）の混合溶液に滴下し、室温で３時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をエーテル－ヘキサンで再結晶し標記化合物５．２ｇ（収率８９．７％）を得た。

【０１６２】ＮＭＲ（$CDCl_3$）δ：１．３９（３Ｈ，ｔ，Ｊ＝７Ｈｚ），４．３６（２Ｈ，Ｊ＝７Ｈｚ），７．１６（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，７Ｈｚ，１Ｈｚ），７．３４－７．４３（２Ｈ，ｍ），７．４５－７．４９（１Ｈ，ｍ），７．６１（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，７Ｈｚ，１Ｈｚ），７．６６（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），８．０９（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），８．９０（１Ｈ，ｄ，Ｊ＝８Ｈｚ）１１．５５（１Ｈ，ｓ）

【０１６３】参考例１５：２－（２－クロロベンズアミド）安息香酸

【０１６４】

【化３６】（２－クロロベンズアミド）安息香酸エチル５．２２ｇ（１７．２ｍｍｏｌ）のエタノール（５０ｍｌ）溶液に１Ｍ－水酸化ナトリウム水溶液５０ｍｌを加え、３時間加熱還流した後、エタノールを減圧下留去した。残留物に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンで再結晶し、標記化合物４．１５ｇ（収率８７．６％）を得た。

【０１６５】ＮＭＲ（$DMSO-d_6$）δ：７．２２（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，８Ｈｚ，１Ｈｚ），７．４９（１Ｈ，ｄｄｄ，Ｊ＝７，７Ｈｚ，１Ｈｚ），７．５５（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，８Ｈｚ，１Ｈｚ），７．５８－７．６８（２Ｈ，ｍ），７．７０（１Ｈ，ｄｄ，Ｊ＝７，１Ｈｚ），８．０３（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），８．６０（１Ｈ，ｄ，Ｊ＝８Ｈｚ），１１．９５（１Ｈ，ｓ）

【０１６６】実施例１９：２－（２－ヘキシルアミノベンズアミド）安息香酸

【０１６７】

【化３７】参考例１５で製造した２－（２－クロロベンズアミド）安息香酸４００ｍｇ（１．４５ｍｍｏｌ）のヘキシルアミン（６ｍｌ）溶液に炭酸カリウム２４０ｍｇ（１．７４ｍｍｏｌ）及び５ｗｔ．％の活性化銅を加え、封管中１７０℃で１．５時間加熱撹拌した後、室温まで冷却した。反応溶液に１Ｍ－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エタノールで再結晶し、標記化合物３７０ｍｇ（収率７５．８％）を得た。

【０１６８】ＮＭＲ（$CDCl_3$）δ：０．９０（３

H，t，J＝7Hz），1．28－1．50（6H，m），1．64－1．74（2H，m），3．19（2H，t，J＝7Hz），6．67（1H，ddd，J＝8Hz，8Hz，1Hz），6．74（1H，d，J＝8Hz），7．14（1H，ddd，J＝8Hz，8Hz，1Hz），7．36（1H，ddd，J＝8Hz，8Hz，1Hz），7．64（1H，ddd，J＝8Hz，8Hz，1Hz），7．68（1H，dd，J＝8Hz，1Hz），8．16（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．52（1H，s）

IR（ν，cm^{-1}，KBr）：2924，2856，1698，1646，1612，1574，1538，1294，1222，756，740

EI－MS（m／z，%）：340（m+，94），322（13），269（75），251（26），204（32），132（100），120（30）

融点：151－152℃

【0169】実施例20：2－［2－（2，2－ジメチルプロピルアミノ）ベンズアミド］安息香酸

【0170】

【化38】参考例15で製造した2－（2－クロロベンズアミド）安息香酸400mg（1．45mmol）の2，2－ジメチルプロピルアミン（7ml）溶液に炭酸カリウム240mg（1．74mmol）及び5wt．%の活性化銅を加え、封管中170℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エーテルーヘキサンで再結晶し、標記化合物170mg（収率36．3%）を得た。

【0171】NMR（$CDCl_3$）δ：1．06（9H，m），2．99（2H，s），6．64（1H，ddd，J＝8Hz，8Hz，1Hz），7．13（1H，ddd，J＝8Hz，8Hz，1Hz），7．34（1H，ddd，J＝8Hz，7Hz，1Hz），7．65（1H，ddd，J＝8Hz，7Hz，1Hz），7．70（1H，dd，J＝8Hz，1Hz），8．16（1H，dd，J＝8Hz，1Hz），8．83（1H，dd，J＝8Hz，1Hz），11．57（1H，s）

IR（ν，cm^{-1}，KBr）：3368，2960，1666，1578，1526，1262，758，746

EI－MS（m／z，%）：326（m+，47），269（89），251（22），132（100），120（23）

融点：193－194℃

【0172】実施例21：2－（2－オクチルアミノベンズアミド）安息香酸

【0173】

【化39】参考例15で製造した2－（2－クロロベンズアミド）安息香酸0．40g（1．45mmol）のオクチルアミン（4ml）溶液に炭酸カリウム0．24g（1．74mmol）及び5wt．%の活性化銅を加え、170℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エタノールで再結晶し、標記化合物0．25g（収率45．9%）を得た。

【0174】NMR（$CDCl_3$）δ：0．89（3H，t，J＝7Hz），1．24－1．39（8H，m），1．39－1．49（2H，m），1．65－1．75（2H，m），3．19（2H，t，J＝7Hz），6．67（1H，ddd，J＝8Hz，8Hz，1Hz），6．75（1H，d，J＝8Hz），7．14（1H，ddd，J＝8Hz，8Hz，1Hz），7．36（1H，ddd，J＝8Hz，7Hz，1Hz），7．64（1H，ddd，J＝8Hz，7Hz，1Hz），7．69（1H，dd，J＝8Hz，1Hz），8．17（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．67（1H，s）

IR（ν，cm^{-1}，KBr）：3228，2928，2852，1698，1646，1610，1574，1540，1292，1204，756，738

EI－MS（m／z，%）：368（m+，90），340（25），269（96），251（22），132（100），120（30）

融点：146－147℃

【0175】実施例22：2－（2－デシルアミノベンズアミド）安息香酸

【0176】

【化40】参考例15で製造した2－（2－クロロベンズアミド）安息香酸400mg（1．45mmol）のデシルアミン（4ml）溶液に炭酸カリウム240mg（1．74mmol）及び5wt．%の活性化銅を加え、170℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、アセトニトリルで再結晶し、標記化合物300mg（収率51．9%）を得た。

【0177】NMR（$CDCl_3$）δ：0．88（3H，t，J＝7Hz），1．20－1．38（12H，m），1．38－1．48（2H，m），1．65－

1．74（2H，m），3．18（2H，t，J＝7Hz），6．66（1H，ddd，J＝8Hz，8Hz，1Hz），6．75（1H，d，J＝8Hz），7．13（1H，ddd，J＝8Hz，8Hz，1Hz），7．35（1H，ddd，J＝8Hz，7Hz，1Hz），7．64（1H，ddd，J＝8Hz，7Hz，1Hz），7．69（1H，dd，J＝8Hz，1Hz），8．15（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．58（1H，s）

IR（ν，cm^{-1}，KBr）：3326，2924，2852，1698，1646，1610，1574，1540，1294，1200，756，736

EI－MS（m／z，%）：396（m+，74），368（28），340（11），269（100），251（26），132（78），120（30）

融点：126－127℃

【0178】参考例16：2－（2－イソインドリルベンズアミド）安息香酸エチル

【0179】

【化41】2－（2－アミノベンズアミド）安息香酸エチル500mg（1．76mmol）のN，N－ジメチルホルムアミド（5ml）溶液に炭酸カリウム530mg（3．87mmol）及びα，α'－ジブロモ－o－キシレン470mg（1．76mmol）を加え、110℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸水溶液を加え酢酸エチルで抽出した。有機層を水及び飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物360mg（収率53．1%）を得た。

【0180】NMR（$CDCl_3$）δ：1．31（3H，t，J＝7Hz），4．22（2H，q，J＝7Hz），4．75（4H，m），6．88（1H，ddd，J＝8Hz，7Hz，1Hz），6．97（1H，d，J＝8Hz），7．13（1H，ddd，J＝8Hz，7Hz，1Hz），7．58－7．65（2H，m），8．05（1H，dd，J＝8Hz，1Hz），8．95（1H，d，J＝8Hz），11．66（1H，s）

【0181】実施例23：2－（2－イソインドリルベンズアミド）安息香酸

【0182】

【化42】参考例16で製造した2－（2－イソインドリルベンズアミド）安息香酸エチル360mg（0．93mmol）のエタノール（5ml）溶液に1M－水酸化ナトリウム水溶液（5ml）を加え、2時間加熱還流した後、エタノールを減圧下留去した。残留物に、氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンで再結晶し、標記化合物260mg（収率77．7%）を得た。

【0183】NMR（$CDCl_3$）δ：4．71（4H，s），6．90（1H，ddd，J＝8Hz，7Hz，1Hz），6．99（1H，d，J＝8Hz），7．13－7．23（5H，m），7．40（1H，ddd，J＝8Hz，7Hz，1Hz），7．63（1H，dd，J＝7，1Hz），7．67（1H，ddd，J＝8Hz，7Hz，1Hz），8．08（1H，dd，J＝8Hz，1Hz），8．97（1H，d，J＝8Hz），11．48（1H，s）

IR（ν，cm^{-1}，KBr）：3328，1668，1518，1264，756

EI－MS（m／z，%）：358（m+，15），312（7），269（10），221（52），193（100），132（14）

融点：185－186℃

【0184】実施例24：2－［2－（1－プロピルブチル）アミノベンズアミド］安息香酸

【0185】

【化43】参考例15で製造した2－（2－クロロベンズアミド）安息香酸0．26g（0．93mmol）の4－ヘプチルアミン（3ml）溶液に炭酸カリウム0．15g（1．11mmol）及び5wt．%の活性化銅を加え、封管中170℃で5時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物0．15g（収率45．0%）を得た。

【0186】NMR（$CDCl_3$）δ：0．92（6H，t，J＝7Hz），1．30－1．62（8H，m），3．50（1H，pent，J＝6Hz），6．61（1H，ddd，J＝8Hz，7Hz，1Hz），6．75（1H，d，J＝8Hz），7．13（1H，ddd，J＝8Hz，7Hz，1Hz），7．32（1H，ddd，J＝8Hz，7Hz，1Hz），7．68（1H，dd，J＝8Hz，1Hz），8．79（1H，dd，J＝8Hz，1Hz），11．55（1H，s）

IR（ν，cm^{-1}，KBr）：2956，2928，1652，1602，1578，1532，1256，752，742

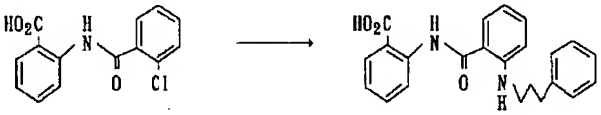
EI－MS（m／z，%）：354（m+，22），311（75），293（6），174（100），146（19），132（13）

融点：139－140℃

【0187】実施例25：2－［2－（1－メチルヘキシル）アミノベンズアミド］安息香酸

【0188】
【化44】参考例15で製造した2－（2－クロロベンズアミド）安息香酸0．35g（1．27mmol）の2－アミノヘプタン（3ml）溶液に炭酸カリウム0．21g（1．52mmol）及び5wt．%の活性化銅を加え、封管中170℃で5時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、ヘキサンで再結晶し、標記化合物0．23g（収率50．4%）を得た。
【0189】NMR（$CDCl_3$）δ：0．88（3H，t，J＝7Hz），1．24（3H，d，J＝6Hz），1．26－1．56（7H，m），1．58－1．70（1H，m），3．56（1H，q，J＝6Hz），6．63（1H，dd，J＝7Hz、7Hz），6．74（1H，d，J＝8Hz），7．10－7．16（1H，m），7．30－7．38（1H，m），7．60－7．66（1H，m），7．69（1H，dd，J＝8Hz，1Hz），8．15（1H，dd，J＝8Hz，1．Hz），8．79（1H，d，J＝8Hz），11．54（1H，s）
IR（ν，cm^{-1}，KBr）：2952，2932，1698，1652，1612，1574，1538，1264，756，742
EI－MS（m／z，%）：354（m+，22），336（4），311（28），283（67），174（100），146（19），132（13）
融点：108－109℃
【0190】実施例26：2－［2－（2－エチルヘキシル）アミノベンズアミド］安息香酸
【0191】
【化45】

【0192】参考例15で製造した2－（2－クロロベンズアミド）安息香酸0．40g（1．45mmol）の2－エチルヘキシルアミン（3ml）溶液に炭酸カリウム0．24g（1．74mmol）及び5wt．%の活性化銅を加え、封管中170℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、酢酸エチルーヘキサンで再結晶し、標記化合物0．25g（収率47．4%）を得た。
【0193】NMR（$CDCl_3$）δ：0．86－0．96（6H，m），1．26－1．54（8H，m），1．61－1．72（1H，m），3．09（1H，dd，J＝12Hz，6Hz），3．11（1H，dd，J＝12Hz，6Hz），6．63－6．68（1H，m），6．74（1H，d，J＝8Hz），7．13（1H，ddd，J＝8Hz，7Hz，1Hz），7．36（1H，ddd，J＝8Hz，7Hz，1Hz），7．64（1H，ddd，J＝8Hz，7Hz，1Hz），7．69（1H，dd，J＝7，1Hz），8．16（1H，dd，J＝8Hz，1Hz），8．82（1H，dd，J＝8Hz，1Hz），11．55（1H，s）
IR（ν，cm^{-1}，KBr）：2960，2924，1654，1602，1530，1256，788，746
EI－MS（m／z，%）：368（m+，23），269（70），251（18），174（3），146（5），132（100），120（28）
融点：120－121℃
【0194】実施例27：2－［2－（3－フェニルプロピル）アミノベンズアミド］安息香酸
【0195】
【化46】



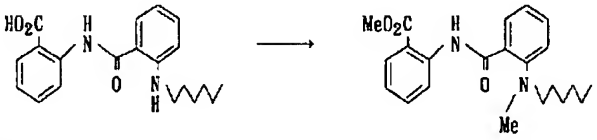
【0196】参考例15で製造した2－（2－クロロベンズアミド）安息香酸0．30g（1．09mmol）の3－フェニルプロピルアミン（3ml）溶液に炭酸カリウム0．18g（1．31mmol）及び5wt．%の活性化銅を加え、170℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物0．18g（収率42．9%）を得た。
【0197】NMR（$CDCl_3$）δ：1．98－2．08（2H，m），2．77（2H，t，J＝7Hz），3．21（2H，t，J＝7Hz），6．64－6．72（2H，m），7．10－7．24（4H，

m），7．24－7．36（3H，m），7．61－7．67（1H，m），7．70（1H，dd，J＝8Hz，1Hz），8．15（1H，dd，J＝8Hz，1Hz），8．82（1H，d，J＝8Hz），11．61（1H，s）
IR（ν，cm^{-1}，KBr）：2920，1650，1602，1574，1534，1262，758
EI－MS（m／z，%）：374（m+，51），356（3），269（69），251（22），174（5），146（14），132（100），120（36）
融点：202－203℃

【0198】参考例17：2－［2－（N－メチルヘキシルアミノ）ベンズアミド］安息香酸メチル

【0199】

【化47】



【0200】実施例19で製造した2－（2－ヘキシルアミノベンズアミド）安息香酸0．15g（0．44mmol）のN，N－ジメチルホルムアミド（5ml）溶液に炭酸カリウム0．13g（0．97mmol）及びヨードメタン0．1ml（1．76mmol）を加え、50℃で17時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物0．14g（収率85．7%）を得た。

【0201】NMR（$CDCl_3$）δ：0．78（3H，t，J＝7Hz），1．10－1．22（6H，m），1．40－1．50（2H，m），2．83（3H，s），2．97－3．04（2H，m），3．88（3H，s），7．07－7．14（2H，m），7．17（1H，d，J＝8Hz），7．41（1H，ddd，J＝8Hz，7Hz，1Hz），7．54－7．60（1H，m），7．98（2H，ddd，J＝9，8，1Hz），8．86（1H，d，J＝8Hz），12．58（1H，s）

【0202】実施例28：2－［2－（N メチルヘキシルアミノ）ベンズアミド］安息香酸

【0203】

【化48】

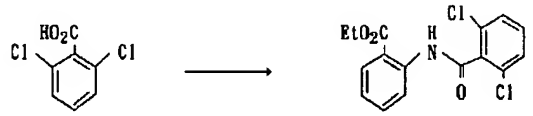
【0204】参考例17で製造した2－［2－（N－メチルヘキシルアミノ）ベンズアミド］安息香酸メチル0．14g（0．38mmol）のエタノール（5ml）溶液に1M－水酸化ナトリウム水溶液5mlを加え、2時間加熱還流した後、エタノールを減圧下留去した。残留物に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンで再結晶し、標記化合物0．09g（収率68．1%）を得た。

【0205】NMR（$CDCl_3$）δ：0．71－0．77（3H，m），1．05－1．15（6H，m），1．38－1．50（2H，m），2．78（3H，s），2．92－3．00（2H，m），7．08－7．18（3H，m），7．38－7．66（1H，m），7．98（1H，dd，J＝8Hz，1Hz），8．08（1H，dd，J＝J＝8Hz，1Hz），8．87（1H，d，J＝8Hz）
IR（ν，cm^{-1}，KBr）：2928，1664，1586，1516，1234，756
EI－MS（m／z，%）：354（m+，22），283（42），265（46），218（69），217（93），146（46），134（100），132（67）

【0206】参考例18：2－（2，6－ジクロロベンズアミド）安息香酸エチル

【0207】

【化49】



【0208】2，6－ジクロロ安息香酸3．0g（15．7mmol）の無水ベンゼン溶液（20ml）に塩化チオニル2．0ml及びN，N－ジメチルホルムアミド数滴を加え、2時間加熱還流した後、溶媒を減圧下留去した。残留物を酢酸エチル（20ml）に溶解し、これを氷冷下炭酸カリウム4．3g（31．4mmol）及び2－アミノ安息香酸エチル2．3ml（15．7mmol）の水（30ml）及び酢酸エチル（20ml）の混合溶液に滴下し、室温で42時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマ

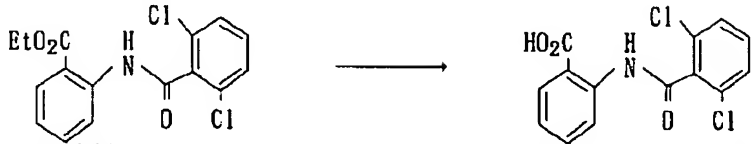
トグラフィーで精製した後、酢酸エチルーヘキサンで再結晶し標記化合物2．8g（収率53．6%）を得た。

【0209】NMR（$CDCl_3$）δ：1．39（3H，t，J＝7Hz），4．34（2H，J＝7Hz），7．16－7．22（1H，m），7．30（1H，dd，J＝9Hz，2Hz），7．61－7．67（1H，m），8．10（1H，dd，J＝8Hz，1Hz），8．90（1H，dd，J＝8Hz，1Hz），11．39（1H，s）

【0210】参考例19：2－（2，6－ジクロロベンズアミド）安息香酸

【0211】

【化50】



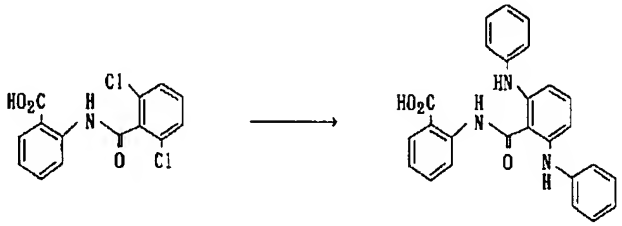
【0212】参考例18で製造した（2，6－ジクロロベンズアミド）安息香酸エチル2．82g（8．34mmol）のエタノール（20ml）溶液に1M－水酸化ナトリウム水溶液（20ml）を加え、6時間加熱還流した後、エタノールを減圧下留去した。残留物に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し、標記化合物2．08g（収率80．3%）を得た。

【0213】NMR（DMSO－d_6）δ：7．28（1H，ddd，J＝8Hz，8Hz，1Hz），7．55（1H，dd，J＝9Hz，7Hz），7．60－7．65（2H，m），7．70（1H，ddd，J＝9Hz，8Hz，1Hz），8．03（1H，dd，J＝8Hz，1Hz），8．55（1H，dd，J＝8Hz，1Hz），11．56（1H，s）

【0214】実施例29：2－（2，6－ジフェニルアミノベンズアミド）安息香酸

【0215】

【化51】



【0216】参考例19で製造した2－（2，6－ジクロロベンズアミド）安息香酸0．30g（0．97mmol）のアニリン（3ml）溶液に炭酸カリウム0．32g（2．32mmol）及び5wt．%の活性化銅を加え、4時間加熱還流した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製したのち、酢酸エチルーヘキサンで再結晶し、標記化合物0．13g（収率30．8%）を得た。

【0217】NMR（$CDCl_3$）δ：6．83（2H，d，J＝8Hz），6．89－6．95（2H，m），7．06－7．16（6H，m），7．20－7．28（4H，m），7．53－7．59（1H，m），8．04（1H，dd，J＝8Hz，1Hz），8．72（1H，d，J＝8Hz），11．53（1H，s）

IR（ν，cm^{-1}，KBr）：2960，1680，1658，1574，1508，1262，752

EI－MS（m／z，%）：439（m+，57），421（10），368（8），303（23），302（22），276（73），231（52），205（100）

融点：110－111℃

【0218】実施例30：2－（2，6－ジヘキシルアミノベンズアミド）安息香酸

【0219】

【化52】

【0220】参考例19で製造した2－（2，6－ジクロロベンズアミド）安息香酸0．30g（0．97mm

ｏｌ）のヘキシルアミン（３ｍｌ）溶液に炭酸カリウム０．３２ｇ（２．３２ｍｍｏｌ）及び５ｗｔ．％の活性化銅を加え、封管中１７０℃で３時間加熱撹拌した後、室温まで冷却した。反応溶液に１Ｍ－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、エーテル－ヘキサンで再結晶し、標記化合物０．２１ｇ（収率４９．９％）を得た。

【０２２１】ＮＭＲ（$CDCl_3$）δ：０．８２（３Ｈ，ｔ，Ｊ＝７Ｈｚ），１．１９－１．３９（６Ｈ，ｍ），１．５６－１．６２（２Ｈ，ｍ），３．０８（２Ｈ，ｔ，Ｊ＝７Ｈｚ），６．１０（２Ｈ，ｄ，Ｊ＝８Ｈｚ），７．０９－７．１７（２Ｈ，ｍ），７．６２（１Ｈ，ｄｄｄ，Ｊ＝８Ｈｚ，８Ｈｚ，１Ｈｚ），８．０９（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８Ｈｚ）

ＩＲ（ν，cm^{-1}，ＫＢｒ）：１６８２，１６４６，１５８０，１５２０，１２７０，７４８

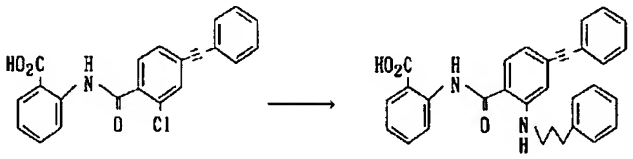
ＥＩ－ＭＳ（ｍ／ｚ，％）：４２３（ｍ＋，２７），４０５（１３），３６８（１００），２８６（４２），２３６（４５）

融点：１９５－１９７℃

【０２２２】実施例３１：２－［４－フェニルエチニル－２－（３－フェニルプロピルアミノ）ベンズアミド］安息香酸

【０２２３】

【化５３】



【０２２４】参考例１０で製造した２－（２－クロロ－４－フェニルエチニルベンズアミド）安息香酸０．４０ｇ（１．０６ｍｍｏｌ）の３－フェニルプロピルアミン（３ｍｌ）溶液に炭酸カリウム０．１８ｇ（１．２８ｍｍｏｌ）及び５ｗｔ．％の活性化銅を加え、１８０℃で３時間加熱撹拌した後、室温まで冷却した。反応溶液に１Ｍ－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、メタノールで再結晶し標記化合物０．３０ｇ（収率５９．２％）を得た。

【０２２５】ＮＭＲ（$CDCl_3$）δ：２．０６（２Ｈ，ｐｅｎｔ，Ｊ＝７Ｈｚ），２．７８（２Ｈ，ｔ，Ｊ＝７Ｈｚ），３．２３（２Ｈ，ｔ，Ｊ＝７Ｈｚ），６．８２－６．８７（２Ｈ，ｍ），７．１３－７．３２（７Ｈ，ｍ），７．３４－７．３９（３Ｈ，ｍ），７．５４－７．５８（２Ｈ，ｍ），７．６２－７．６９（２Ｈ，ｍ），８．１８（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），８．８１（１Ｈ，ｄ，Ｊ＝８Ｈｚ），１１．６２（１Ｈ，ｓ）

ＩＲ（ν，cm^{-1}，ＫＢｒ）：２９３６，１６５０，１６０４，１５８６，１５３８，１２６０，７５４

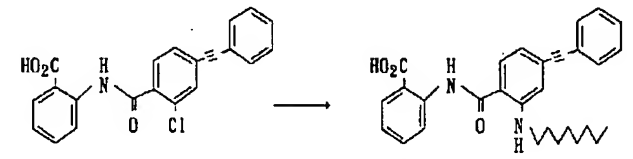
ＥＩ－ＭＳ（ｍ／ｚ，％）：４７４（ｍ＋，８０），４５６（５７），３７４（２０），３５１（５０），２６９（２３），２３２（１００），１７６（２７），１３２（４１），１２０（２２），９１（７２）

融点：１９９－２００℃

【０２２６】実施例３２：２－（２－オクチルアミノ－４－フェニルエチニルベンズアミド）安息香酸

【０２２７】

【化５４】



【０２２８】参考例１０で製造した２－（２－クロロ－４－フェニルエチニルベンズアミド）安息香酸０．４０ｇ（１．０６ｍｍｏｌ）のオクチルアミン（３ｍｌ）溶液に炭酸カリウム０．１８ｇ（１．２８ｍｍｏｌ）及び５ｗｔ．％の活性化銅を加え、１８０℃で３時間加熱撹拌した後、室温まで冷却した。反応溶液に１Ｍ－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、酢酸エチル－ヘキサンで再結晶し標記化合物０．０５ｇ（収率９．６％）を得た。

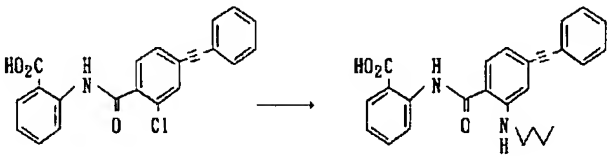
【０２２９】ＮＭＲ（$CDCl_3$）δ：０．８８（３Ｈ，ｔ，Ｊ＝７Ｈｚ），１．２２－１．４０（８Ｈ，ｍ），１．４０－１．５０（２Ｈ，ｍ），１．７８（２Ｈ，ｐｅｎｔ，Ｊ＝７Ｈｚ），３．２０（２Ｈ，ｔ，Ｊ＝７Ｈｚ），６．８３（１Ｈ，ｄｄ，Ｊ＝８Ｈｚ，１Ｈｚ），６．８９（１Ｈ，ｄ，Ｊ＝１Ｈｚ），７．１２－７．１８（１Ｈ，ｍ），７．３４－７．４０（３Ｈ，ｍ），７．５６－７．６０（２Ｈ，ｍ），７．６３－７．６９（２Ｈ，ｍ），８．１７（１Ｈ，ｄｄ，Ｊ＝８

Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．59（1H，s）
IR（ν，cm^{-1}，KBr）：2924，1656，1604，1564，1520，1254，752
EI－MS（m／z，%）：450（M－H8，49），421（10），368（18），351（72），176（15）
融点：162－163℃

【0230】実施例33：2－（2－ブチルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0231】

【化55】



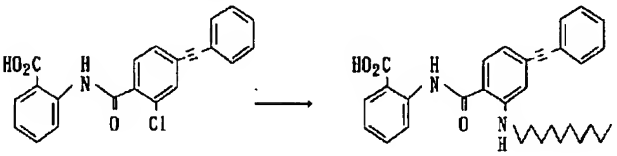
【0232】参考例10で製造した2－（2－クロロ－4－フェニルエチニルベンズアミド）安息香酸0．30g（0．80mmol）のブチルアミン（2ml）溶液に炭酸カリウム0．13g（0．96mmol）及び5wt．%の活性化銅を加え、封管中180℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し標記化合物018g（収率53．2%）を得た。

【0233】NMR（$CDCl_3$）δ：0．98（3H，t，J＝7Hz），1．44－1．54（2H，m），1．66－1．76（2H，m），3．02（2H，t，J＝7Hz），6．83（1H，dd，J＝8Hz，1Hz），6．89（1H，d，J＝1Hz），7．12－7．18（1H，m），7．33－7．40（3H，m），7．54－7．60（2H，m），7．62－7．68（2H，m），8．17（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．59（1H，s）
IR（ν，cm^{-1}，KBr）：3438，2956，1680，1650，1540，1262，754
EI－MS（m／z，%）：412（m+，69），394（12），369（22），276（33），232（100），176（23）
融点：217－219℃

【0234】実施例34：2－（3－デシルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0235】

【化56】



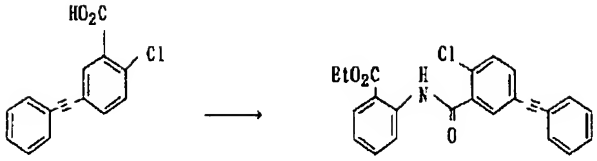
【0236】参考例10で製造した2－（2－クロロ－4－フェニルエチニルベンズアミド）安息香酸0．30g（0．80mmol）のデシルアミン（3ml）溶液に炭酸カリウム0．13g（0．96mmol）及び5wt．%の活性化銅を加え、180℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、酢酸エチルーヘキサンで再結晶し標記化合物0．08g（収率18．9%）を得た。

【0237】NMR（$CDCl_3$）δ：0．87（3H，t，J＝7Hz），1．20－1．40（12H，m），1．40－1．50（2H，m），1．66－1．76（2H，m），3．20（2H，t，J＝7Hz），6．83（1H，dd，J＝8Hz，1Hz），6．89（1H，d，J＝1），7．12－7．18（1H，m），7．23－7．40（3H，m），7．53－7．59（2H，m），7．62－7．68（2H，m），8．17（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．60（1H，s）
IR（ν，cm^{-1}，KBr）：2924，1652，1608，1538，1258，764，754
EI－MS（m／z，%）：496（m+，42），478（87），369（26），351（100），323（30），232（45）
融点：144－146℃

【0238】参考例20：2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸エチル

【0239】

【化57】



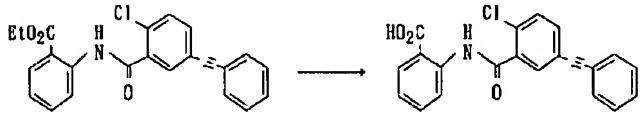
【0240】2－クロロ－5－フェニルエチニル安息香酸2．0g（7．79mmol）の無水ベンゼン溶液（15ml）に塩化チオニル1．0ml及びN，N－ジメチルホルムアミド数滴を加え、1時間加熱還流した後、溶媒を減圧下留去した。残留物を酢酸エチル（20ml）に溶解し、これを氷冷下炭酸カリウム2．1g（15．6mmol）及びアミノ安息香酸エチル1．1ml（7．79mmol）の水（15ml）及び酢酸エチル（10ml）の混合溶液に滴下し、室温で2時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し標記化合物1．7g（収率53．4%）を得た。

【0241】NMR（$CDCl_3$）δ：1．40（3H，t，J＝7Hz），4．37（2H，q，J＝7Hz），7．14－7．20（1H，m），7．33－7．38（3H，m），7．45（1H，d，J＝8Hz），7．50－7．56（3H，m），7．60－7．66（1H，m），7．80（1H，d，J＝2Hz），8．10（1H，dd，J＝8Hz，1Hz），8．88（1H，d，J＝8Hz），11．57（1H，s）

【0242】参考例21：2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸

【0243】

【化58】



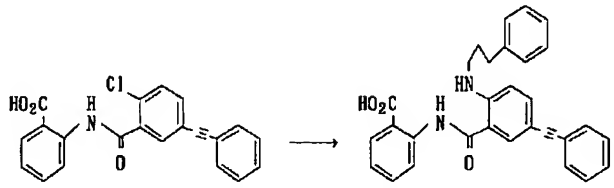
【0244】参考例20で製造した2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸エチル1．68g（4．16mmol）のエタノール（15ml）溶液に1M－水酸化ナトリウム水溶液20mlを加え、2時間加熱還流した後、エタノールを減圧下留去した。残留物に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し、標記化合物1．53g（収率97．8%）を得た。

NMR（DMSO－d_6）δ：7．24－7．30（1H，m），7．43－7．48（3H，m），7．57－7．63（2H，m），7．65－7．74（3H，m），7．91（1H，d，J＝2Hz），8．03（1H，dd，J＝8Hz，1Hz），8．50（1H，d，J＝8Hz），11．61（1H，s），13．71（1H，br－s）

【0245】実施例35：2－［5－フェニルエチニル－2－（3－フェニルプロピル）アミノベンズアミド］安息香酸

【0246】

【化59】



【0247】参考例21で製造した2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸0．30g（0．80mmol）の3－フェニルプロピルアミン（1．5ml）溶液に炭酸カリウム0．13g（0．96mmol）及び5wt．%の活性化銅を加え、180℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、酢酸エチルーヘキサンで再結晶し標記化合物0．15g（収率38．6%）を得た。

【0248】NMR（$CDCl_3$）δ：2．00－2．09（2H，m），2．78（2H，t，J＝7Hz），3．24（2H，t，J＝7Hz），6．65（1H，d，J＝8Hz），6．95－7．02（1H，m），7．17－7．33（8H，m），7．46－7．55（3H，m），7．58－7．64（1H，m），7．91（1H，d，J＝2Hz），8．01（1H，d，J＝8Hz），8．79（1H，d，J＝

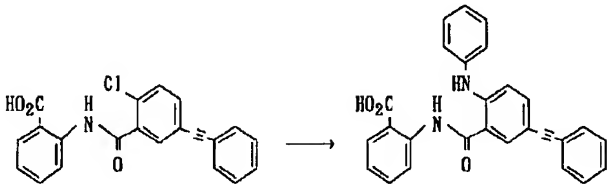
8Hz），11．70（1H，s）
IR（ν，cm^{-1}，KBr）：2928，1658，1604，1532，1262，756
EI－MS（m／z，%）：474（m+，9），456（100），383（36），351（46），232（9）

融点：194－196℃

【0249】実施例36：2－（2－フェニルアミノ－5－フェニルエチニルベンズアミド）安息香酸

【0250】

【化60】



【0251】参考例21で製造した2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸0．30g（0．80mmol）の3－フェニルプロピルアミン（1．5ml）溶液に炭酸カリウム0．13g（0．96mmol）及び5wt．%の活性化銅を加え、180℃で1．5時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、酢酸エチルーヘキサンで再結晶し標記化合物0．17g（収率50．7%）を得た。

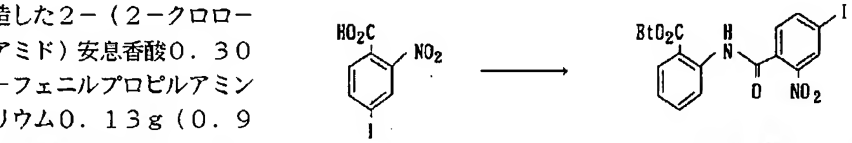
【0252】NMR（$CDCl_3$）δ：6．99－7．04（1H，m），7．07－7．12（1H，m），7．22－7．39（8H，m），7．46（1H，dd，J＝8Hz，2Hz），7．50－7．56（2H，m），7．61－7．66（1H，m），7．97（1H，d，J＝2Hz），8．04（1H，dd，J＝8Hz，1Hz），8．81（1H，d，J＝8Hz），9．81（1H，s），11．79（1H，s）
IR（ν，cm^{-1}，KBr）：1682，1646，1580，1520，1270，748
EI－MS（m／z，%）：423（m+，27），405（13），368（100），286（42），236（45）

融点：199－202℃

【0253】参考例22：2－（4－ヨード－2－ニトロベンズアミド）安息香酸エチル

【0254】

【化61】



【0255】4－ヨード－2－ニトロ安息香酸1．82g（6．21mmol）の無水ベンゼン溶液（10ml）に塩化チオニル1．0ml及びN，N－ジメチルホルムアミド数滴を加え、1時間加熱還流した後、溶媒を減圧下留去した。残留物を酢酸エチル（15ml）に溶解し、これを氷冷下炭酸カリウム1．8g（13．05mmol）及び2－アミノ安息香酸エチル0．97ml（6．52mmol）の水（15ml）及び酢酸エチル（5ml）の混合溶液に滴下し、室温で16時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し標記化合物2．25g（収率82．3%）を得た。

【0256】NMR（$CDCl_3$）δ：1．40（3H，t，J＝7Hz），4．35（2H，J＝7Hz），7．16－7．21（1H，m），7．44（1H，d，J＝8Hz），7．59－7．65（1H，m），8．05－8．12（2H，m），8．39（1H，d，J＝1Hz），8．77（1H，d，J＝8Hz），11．66（1H，s）

【0257】参考例23：2－（2－アミノ－4－ヨードベンズアミド）安息香酸エチル

【0258】

【化62】

【0259】参考例22で製造した2－（4－ヨード－2－ニトロベンズアミド）安息香酸エチル2．25g（5．11mmol）のエタノール（10ml）溶液に20%アンモニウムサルファイド水溶液10mlを滴下し、4時間加熱還流した。反応溶液を氷冷し、不要物を沪過した。沪液に4M塩酸を加え酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水にて順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去

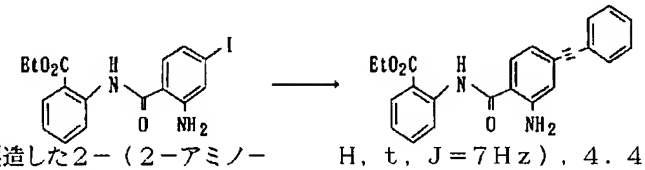
した。残留物を塩化メチレンで再結晶し標記化合物0．97g（収率46．5%）を得た。

【0260】NMR（$CDCl_3$）δ：1．42（3H，t，J=7Hz），4．41（2H，J=7Hz），7．07－7．14（3H，m），7．41（1H，d，J=8Hz），7．58（1H，ddd，J=8Hz，7Hz，1Hz），8．09（1H，dd，J=8Hz，1Hz），8．77（1H，J=8Hz，1Hz），11．88（1H，s）

【0261】参考例24：2－（2－アミノ－4－フェニルエチニルベンズアミド）安息香酸エチル

【0262】

【化63】



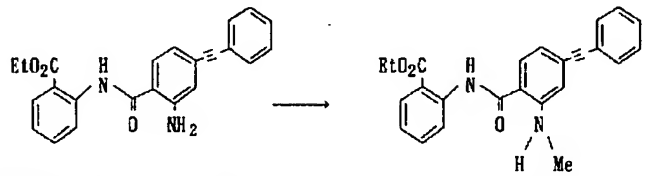
【0263】参考例23で製造した2－（2－アミノ－4－ヨードベンズアミド）安息香酸エチル0．97g（2．36mmol）のジエチルアミン（10ml）溶液に窒素雰囲気下フェニルアセチレン0．4ml（3．55mmol）、ジクロロビストリフェニルホスフィンパラジウム0．02g（0．02mmol）及びヨウ化銅0．01g（0．04mmol）を加え、室温で1時間撹拌した後、ジエチルアミンを減圧下留去した。残留物に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をクロロホルム－ヘキサンで再結晶し標記化合物0．55g（収率60．9%）を得た。

【0264】NMR（$CDCl_3$）δ：1．43（3H，t，J=7Hz），4．42（2H，q，J=7Hz），6．89（1H，d，J=1Hz），6．92（1H，dd，J=8Hz，1Hz），7．12（1H，ddd，J=8Hz，7Hz，1Hz），7．34－7．38（3H，m），7．51－7．56（2H，m），7．69（1H，ddd，J=8Hz，7Hz，1Hz），7．70（1H，d，J=8Hz），8．10（1H，dd，J=8Hz，1Hz），8．80（1H，dd，J=8Hz，1Hz），11．89（1H，s）

【0265】参考例25：2－（2－メチルアミノ－4－フェニルエチニルベンズアミド）安息香酸エチル

【0266】

【化64】



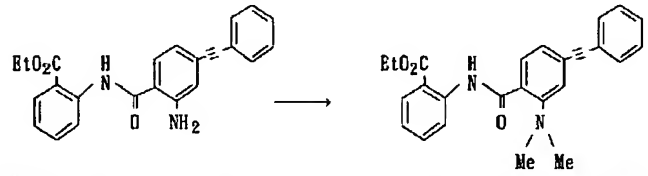
【0267】参考例24で製造した2－（2－アミノ－4－フェニルエチニルベンズアミド）安息香酸エチル0．43g（1．12mmol）のN，N－ジメチルホルムアミド（6ml）溶液に炭酸カリウム300mg（2．24mmol）及びヨードメタン0．2ml（3．36mmol）を加え、室温で7時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーにて精製し、標記化合物0．24g（収率42．0%）を得た。

【0268】NMR（$CDCl_3$）δ：1．43（3H，t，J=7Hz），2．93（3H，d，J=3Hz），4．42（2H，q，J=7Hz），6．84－6．90（2H，m），7．08－7．14（1H，m），7．34－7．39（3H，m），7．54－7．61（3H，m），7．72（1H，d，J=8Hz），7．84－7．94（1H，m），8．10（1H，dd，J=8Hz，1Hz），8．76（1H，dd，J=8Hz，1Hz），11．88（1H，s）

【0269】参考例26：2－（2－ジメチルアミノ－4－フェニルエチニルベンズアミド）安息香酸エチル

【0270】

【化65】



【0271】参考例24で製造した2－（2－アミノ－4－フェニルエチニルベンズアミド）安息香酸エチル0．43g（1．12mmol）のN，N－ジメチルホルムアミド（6ml）溶液に炭酸カリウム300mg（2．24mmol）及びヨードメタン0．2ml（3．36mmol）を加え、室温で17時間撹拌し

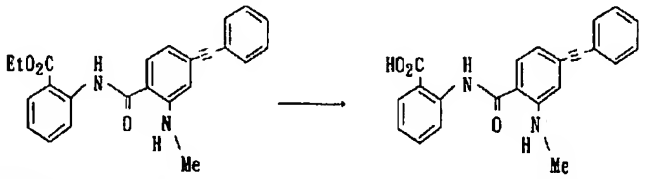
た。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を残留物をシリカゲルクロマトグラフィーにて精製し、標記化合物0．29g（収率63．0%）を得た。

【0272】NMR（$CDCl_3$）δ：1．39（3H，t，J＝7Hz），2．84（6H，s），4．35（2H，q，J＝7Hz），7．11（1H，ddd，J＝8Hz，7Hz，1Hz），7．24－7．27（1H，m），7．30（1H，d，J＝1Hz），7．34－7．40（3H，m），7．53－7．60（3H，m），7．94（1H，d，J＝8Hz），8．03（1H，dd，J＝8Hz，1Hz），8．91－8．94（1H，m），12．59（1H，s）

【0273】実施例37：2－（2－メチルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0274】

【化66】



【0275】参考例25で製造した2－（2－メチルアミノ－4－フェニルエチニルベンズアミド）安息香酸エチル0．06g（0．16mmol）のエタノール（10ml）溶液に1M－水酸化ナトリウム水溶液15mlを加え、4時間加熱還流した後、エタノールを減圧下留去した。残留物に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し、標記化合物0．05g（収率94．0%）を得た。

【0276】NMR（$CDCl_3$）δ：2．94（3H，s），6．86（1H，dd，J＝8Hz，1Hz），6．88（1H，d，J＝1Hz），7．15（1H，ddd，J＝8Hz，7Hz，1Hz），7．34－7．40（3H，m），7．54－7．59（2H，m），7．62－7．67（1H，m），7．66（1H，d，J＝8Hz），8．16（1H，dd，J＝8Hz，1Hz），8．80（1H，dd，J＝8Hz，1Hz），11．66（1H，s）

IR（ν，cm^{-1}，KBr）：3416，1690，1646，1608，1584，1536，1230，752

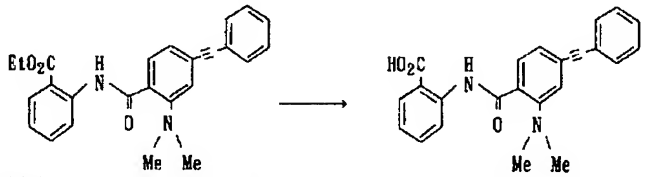
EI－MS（m／z，%）：370（m+，4），352（1），278（1），256（1），234（5）

融点：219－220℃

【0277】実施例38：2－（2－ジメチルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0278】

【化67】



【0279】参考例26で製造した2－（2－ジメチルアミノ－4－フェニルエチニルベンズアミド）安息香酸エチル0．29g（0．71mmol）のエタノール（10ml）溶液に1M－水酸化ナトリウム水溶液10mlを加え、2時間加熱還流した後、エタノールを減圧下留去した。残留物に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をクロロホルムーヘキサンで再結晶し、標記化合物0．19g（収率69．4%）を得た。

【0280】NMR（$CDCl_3$）δ：2．94（6H，s），7．13－7．19（1H，m），7．28（1H，dd，J＝8Hz，1Hz），7．32（1H，d，J＝1Hz），7．35－7．40（3H，m），7．54－7．60（2H，m），7．65（1H，ddd，J＝8Hz，7Hz，1Hz），7．96（1H，d，J＝8Hz），8．12（1H，dd，J＝8Hz，1Hz），8．97（1H，d，J＝8Hz），12．4－12．6（1H，m）

IR（ν，cm^{-1}，KBr）：1696，1652，1586，1522，1196，764，752

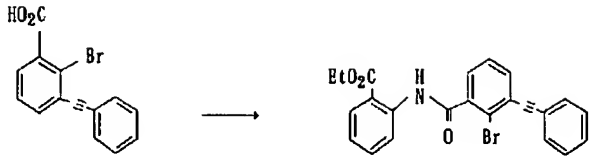
EI－MS（m／z，%）：384（m+，19），366（3），248（100），247（90），191（13），176（11）

融点：186－187℃

【0281】参考例27：2－（2－ブロモ－3－フェニルエチニルベンズアミド）安息香酸エチル

【0282】

【化68】



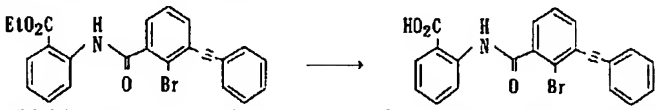
【0283】2－ブロモ－3－フェニルエチニル安息香酸1．53gの無水ベンゼン溶液（10ml）に塩化チオニル1．0ml及びN，N－ジメチルホルムアミド数滴を加え、0．75時間加熱還流した後、溶媒を減圧下留去した。残留物を酢酸エチル（20ml）に溶解し、これを氷冷下炭酸カリウム1．4g（10．16mmol）、2－アミノ安息香酸エチル0．75ml（5．08mmol）の水（15ml）及び酢酸エチル（5ml）の混合溶液に滴下し、室温で17時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し、標記化合物1．80g（収率78．9%）を得た。

【0284】NMR（$CDCl_3$）δ：1．39（3H，t，J＝7Hz），4．35（2H，J＝7Hz），7．14－7．20（1H，m），7．35－7．43（4H，m），7．50（1H，dd，J＝8Hz，1Hz），7．57－7．67（4H，m），8．10（1H，dd，J＝8Hz，1Hz），8．90（1H，d，J＝8Hz），11．48（1H，s）

【0285】参考例28：2－（2－ブロモ－3－フェニルエチニルベンズアミド）安息香酸

【0286】

【化69】



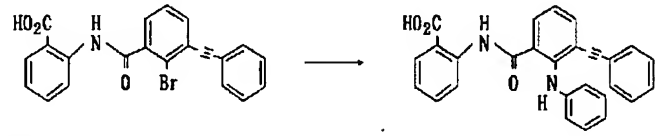
【0287】参考例27で製造した2－（2－ブロモ－3－フェニルエチニルベンズアミド）安息香酸エチル1．79g（3．99mmol）のエタノール（20ml）溶液に1M－水酸化ナトリウム水溶液20mlを加え、2時間加熱撹拌した後、エタノールを減圧下留去した。残留物に氷冷下濃塩酸を滴下し酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水の順で洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し、標記化合物1．52g（収率90．5%）を得た。

【0288】NMR（DMSO－d_6）δ：7．23－7．29（1H，m），7．44－7．52（3H，m），7．56－7．72（5H，m），7．81（1H，dd，J＝8Hz，1Hz），8．03（1H，dd，J＝8Hz，1Hz），8．57（1H，d，J＝8Hz）

【0289】実施例39：2－（2－フェニルアミノ－3－フェニルエチニルベンズアミド）安息香酸

【0290】

【化70】



【0291】参考例28で製造した2－（2－ブロモ－3－フェニルエチニルベンズアミド）安息香酸0．30g（0．71mmol）のアニリン（2ml）溶液に炭酸カリウム0．11g（0．80mmol）及び5wt．%の活性化銅を加え、180℃で2時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンで再結晶し標記化合物0．17g（収率56．3%）を得た。

【0292】NMR（$CDCl_3$）δ：6．82（1H，s），6．93－6．98（1H，m），7．03－7．10（3H，m），7．14－7．28（8H，m），7．38（1H，dd，J＝7，1Hz），7．43－7．48（1H，m），7．79（1H，dd，J＝8Hz，1Hz），7．97（1H，dd，J＝8Hz，1Hz），8．26（1H，d，J＝8Hz），10．82（1H

IR（ν，cm^{-1}，KBr）：　688，1636，1604，1524，　1240，762，740，698

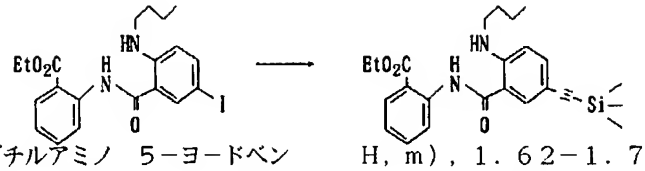
EI－MS（m／z，%）：　32（m+，67），414（5），296（100），267（29）

融点：　57－258℃

【0293】参考例29：2－（2－ブチルアミノ－5－トリメチルシリルエチニルベンズアミド）安息香酸エチル

【0294】

【化71】



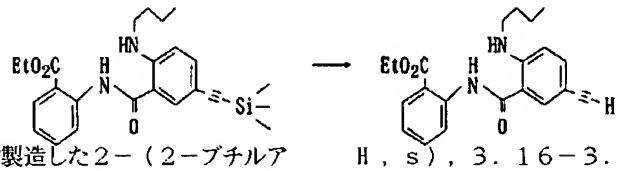
【0295】2－（2－ブチルアミノ　5－ヨードベンズアミド）安息香酸エチル6．45g（13．82mmol）のジエチルアミン（80ml）溶液にトリメチルシリルアセチレン2．3ml（16．59mmol）、ジクロロビストリフェニルホスフィンパラジウム90mg（0．13mmol）及びヨウ化銅50mg（0．26mmol）を加え、室温で1．5時間撹拌した後、ジエチルアミンを減圧下留去した。残留物に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物4．5g（収率74．6%　を得た。

【0296】NMR（$CDCl_3$）δ：0．25（9H，s），0．96（3H，t，J＝7Hz），1．43（3H，t，J＝7Hz），1．42－1．50（2H，m），1．62－1．71（2H，m），3．14－3．22（2H，m），4．42（2H，q，J＝7Hz），6．63（1H，d，J＝9Hz），7．11（1H，ddd，J＝8Hz，7Hz，1Hz），7．42（1H，dd，J＝9Hz，2Hz），7．57（1H，ddd，J＝8Hz，7Hz，1Hz），7．86（1H，d，J＝2Hz），7．95－8．01（1H，m），8．09（1H，dd，J＝8Hz，1Hz），8．65（1H，dd，J＝8Hz，1Hz），11．69（1H，s）

【0297】参考例30：2－（2－ブチルアミノ－5－エチニルベンズアミド）安息香酸エチル

【0298】

【化72】



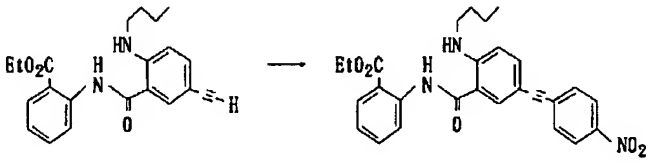
【0299】参考例29で製造した2－（2－ブチルアミノ－5－トリメチルシリルエチニルベンズアミド）安息香酸エチル4．36g（9．99mmol）のテトラヒドロフラン（60ml）溶液に1M－テトラブチルアンモニウムフルオリドテトラヒドロフラン溶液11ml（11．0mmol）を加え、氷冷下1時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物3．06g（収率84．0%）を得た。

【0300】NMR（$CDCl_3$）δ：0．96（3H，t，J＝7Hz），1．40－1．52（5H，m），1．64－1．72（2H，m），2．99（1H，s），3．16－3．23（1H，m），4．43（2H，q，J＝7Hz），6．65（1H，d，J＝9Hz），7．11（1H，ddd，J＝8Hz，7Hz，1Hz），7．44（1H，dd，J＝9Hz，2Hz），7．57（1H，ddd，J＝8Hz，7Hz，1Hz），7．88（1H，d，J＝2Hz），7．98－8．06（1H，m），8．09（1H，dd，J＝8Hz，1Hz），8．68（1H，dd，J＝8Hz，1Hz），11．77（1H，s）

【0301】参考例31：2－［2－ブチルアミノ－5－（4－ニトロフェニル）エチニルベンズアミド］安息香酸エチル

【0302】

【化73】



【0303】参考例30で製造した2－（2－ブチルアミノ－5－エチニルベンズアミド）安息香酸エチル300mg（0．82mmol）のジエチルアミン（10ml）溶液に4－ヨードニトロベンゼン270ml（1．09mmol）、ジクロロビストリフェニルホスフィンパラジウム14mg（0．01mmol）及びヨウ化銅8mg（0．02mmol）を加え、室温で1時間撹拌した後、ジエチルアミンを減圧下留去した。残留物に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物383mg（収率95．8%）を得た。

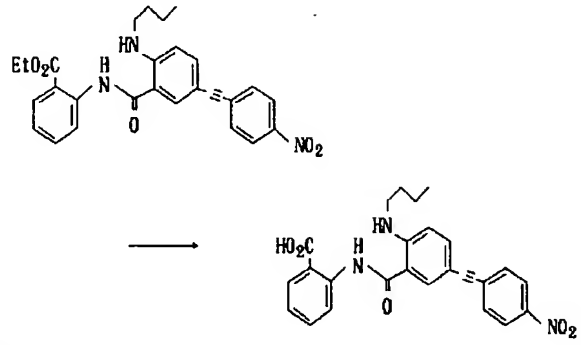
【0304】NMR（$CDCl_3$）δ：0．98（3H，t，J＝7Hz），1．40－1．55（5H，m），1．63－1．74（2H，m），3．17－

3．26（2H，m），4．43（2H，q，J＝7Hz），6．71（1H，d，J＝9Hz），7．11－7．16（1H，m），7．51（1H，dd，J＝9Hz，2Hz），7．57－7．65（3H，m），7．95（1H，d，J＝2Hz），8．10（1H，dd，J＝8Hz，1Hz），8．20（2H，d，J＝9Hz），8．68（1H，d，J＝8Hz），11．82（1H，s）

【0305】実施例40：2－［2－ブチルアミノ－5－（4－ニトロフェニル）エチニルベンズアミド］安息香酸

【0306】

【化74】



【0307】参考例31で製造した2－［2－ブチルアミノ－5－（4－ニトロフェニル）エチニルベンズアミド］安息香酸エチル250mg（0．51mmol）のジオキサン（10ml）溶液に1M－水酸化ナトリウム水溶液2mlを加え、室温で18時間撹拌した。反応溶液に2M－塩酸を加え、酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンにて再結晶し、標記化合物210mg（収率86．4%）を得た。

【0308】NMR（$CDCl_3$）δ：0．99（3H，t，J＝7Hz），1．44－1．54（2H，m），1．67－1．76（2H，m），3．24（2H，t，J＝7Hz），6．72（1H，d，J＝9Hz），6．99－7．05（1H，m），7．50（1H，dd，J＝9Hz，2Hz），7．58（2H，d，J＝9Hz，2Hz），7．63（1H，ddd，J＝8Hz，7Hz，1Hz），7．92（1H，d，J＝2Hz），8．04（1H，dd，J＝8Hz，1Hz），8．09（2H，d，J＝9Hz），8．18－8．30（1H，m），8．78（1H，dd，J＝8Hz，1Hz），11．63（1H，s）

IR（ν，cm^{-1}，KBr）：3452，2964，2196，1658，1588，1520，1340，1258，1218，856，748

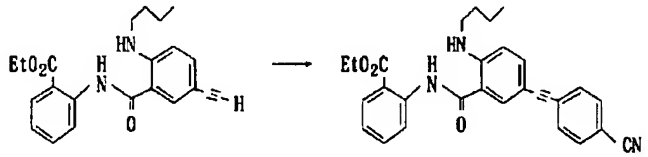
EI－MS（m／z，%）：457（m+，14），439（89），410（25），396（66），368（18），350（13），321（100）

融点：179－180℃

【0309】参考例32：2－［2－ブチルアミノ－5－（4－シアノフェニル）エチニルベンズアミド］安息香酸エチル

【0310】

【化75】



【0311】参考例30で製造した2－（2－ブチルアミノ－5－エチニルベンズアミド）安息香酸エチル300mg（0．82mmol）のジエチルアミン（10ml）溶液に4－ヨードベンゾニトリル250mg（1．09mmol）、ジクロロビストリフェニルホスフィンパラジウム14mg（0．01mmol）及びヨウ化銅8mg（0．02mmol）を加え、室温で2時間撹拌した後、ジエチルアミンを減圧下留去した。残留物に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンにて再結晶し、標記化合物210mg（収率54．7%）を得た。

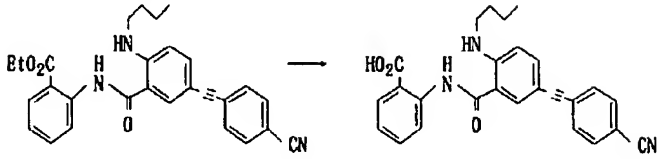
【0312】NMR（$CDCl_3$）δ：0．97（3H，t，J＝7Hz），1．40－1．52（5H，m），1．64－1．74（2H，m），3．22（2H，dt，J＝7Hz，5Hz），4．43（2H，q，J＝7Hz），6．70（1H，d，J＝9Hz），7．11－7．16（1H，m），7．45－7．52（1H，m），7．55－7．64（5H，m），7．93（1H，d，J＝2Hz），8．08－8．16（2H，m），8．68（1H，dd，J＝8

Hz，1Hz），11．80（1H，s）

【0313】実施例41：2－［2－ブチルアミノ－5－（4－シアノフェニル）エチニルベンズアミド］安息香酸

【0314】

【化76】



【0315】参考例32で製造した2－［2－ブチルアミノ－5－（4－シアノフェニル）エチニルベンズアミド］安息香酸エチル210mg（0．45mmol）のジオキサン（10ml）溶液に1M－水酸化ナトリウム水溶液5mlを加え、室温で24時間撹拌した。反応溶液に2M－塩酸を加え、酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物120mg（収率61．0%）を得た。

【0316】NMR（$CDCl_3$）δ：0．99（3H，t，J＝7Hz），1．41－1．54（2H，m），1．67－1．75（2H，m），3．23（2H，t，J＝7Hz），6．71（1H，d，J＝9Hz），7．03－7．09（1H，m），7．49（1H，dd，J＝9Hz，2Hz），7．52－7．56（4H，m），7．65（1H，ddd，J＝8Hz，7Hz，1Hz），7．91（1H，d，J＝2Hz），8．05（1H，dd，J＝8Hz，1Hz），8．78（1H，dd，J＝8Hz，1Hz），11．67（1H，s）

IR（ν，cm^{-1}，KBr）：2964，2248，2204，1654，1598，1530，1298，1218，834，756

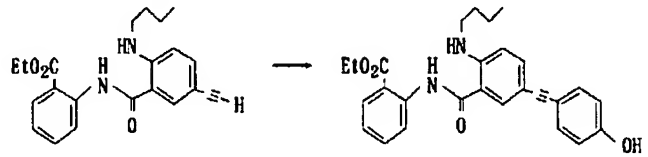
EI－MS（m／z，%）：437（m+，1），419（100），390（24），376（85），348（24）

融点：197－198℃

【0317】参考例33：2－［2－ブチルアミノ－5－（4－ヒドロキシフェニル）エチニルベンズアミド］安息香酸エチル

【0318】

【化77】



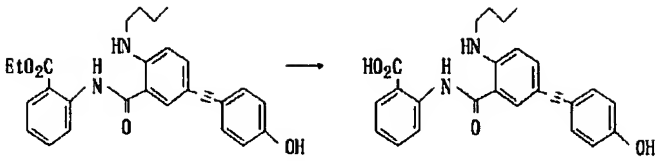
【0319】参考例30で製造した2－（2－ブチルアミノ－5－エチニルベンズアミド）安息香酸エチル300mg（0．82mmol）のジエチルアミン（10ml）溶液に4－t－ブチルジメチルシリルオキシヨードベンゼン410ml（1．23mmol）、ジクロロビストリフェニルホスフィンパラジウム14mg（0．01mmol）及びヨウ化銅8mg（0．02mmol）を加え、室温で19時間撹拌した後、ジエチルアミンを減圧下留去した。反応溶液に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した後、テトラヒドロフラン（10ml）を加え、1M－テトラブチルアンモニウムフルオリドテトラヒドロフラン溶液1．3ml（1．3mmol）を加え、氷冷で1時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物184mg（収率49．0%）を得た。

【0320】NMR（$CDCl_3$）δ：0．97（3H，t，J＝7Hz），1．43（3H，t，J＝7Hz），1．44－1．54（2H，m），1．62－1．72（2H，m），3．17－3．26（2H，m），4．43（2H，q，J＝7Hz），4．90（1H，s），6．68（1H，d，J＝9Hz），6．80（2H，d，J＝9Hz），7．09－7．14（1H，m），7．41（2H，d，J＝9Hz），7．47（1H，dd，J＝9Hz，2Hz），7．55－7．61（1H，m），7．88（1H，d，J＝2Hz），7．94－8．00（1H，m），8．09（1H，dd，8Hz，1Hz），8．67（1H，d，J＝8Hz），11．74（1H，s）

【0321】実施例42：2－［2－ブチルアミノ－5－（4－ヒドロキシフェニル）エチニルベンズアミド］安息香酸

【0322】

【化78】



【0323】参考例33で製造した2－［2－ブチルアミノ－5－（4－ヒドロキシフェニル）エチニルベンズアミド］安息香酸エチル180mg（0．39mmol）のジオキサン（20ml）溶液に1M－水酸化ナトリウム水溶液10mlを加え、室温で4時間撹拌した。反応溶液に2M－塩酸を加え、酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物116mg（収率56．7%）を得た。

【0324】NMR（DMSO－d_6）δ：0．94（3H，t，J＝7Hz），1．36－1．46（2H，m），1．56－1．64（2H，m），3．18－3．24（2H，m），6．76－6．84（3H，m），7．18－7．24（1H，m），7．32（2H，d，J＝9Hz），7．48（1H，dd，J＝9Hz，2Hz），7．61－7．67（1H，m），7．84（1H，d，J＝2Hz），8．00－8．07（2H，m），8．53（1H，dd，J＝8Hz，1Hz），11．96（1H，s）

IR（ν，cm^{-1}，KBr）：3336，2964，1648，1606，1526，1256，1210，836，762

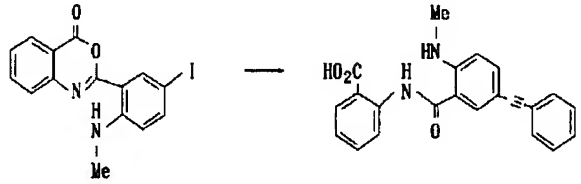
EI－MS（m／z，%）：428（m+，4），410（100），381（6），367（17），321（20）

融点：197－198℃

【0325】実施例43：2－（2－メチルアミノ－5－フェニルエチニルベンズアミド）安息香酸

【0326】

【化79】



【0327】2－（2－メチルアミノ－5－ヨードフェニル）－4－オキソ－4H－3，1－ベンゾキサジン500mg（1．32mmol）のトリエチルアミン（10ml）及びテトラヒドロフラン（15ml）溶液にエチニルベンゼン0．2ml（1．72mmol）、ジクロロビストリフェニルホスフィンパラジウム10mg（0．01mmol）及びヨウ化銅6mg（0．02mmol）を加え、窒素雰囲気下室温で4時間撹拌した後、トリエチルアミンを減圧下留去した。反応溶液に飽和炭酸水素ナトリウム水溶液を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をジオキサン（20ml）に溶解し、1M－水酸化ナトリウム水溶液10mlを加え、室温で18時間撹拌した後、ジオキサンを減圧下留去した。残留物に2M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物340mg（収率69．7%）を得た。

【0328】NMR（DMSO－d_6）δ：2．28（3H，d，J＝5Hz），6．79（1H，d，J＝9Hz），7．18－7．24（1H，m），7．38－7．46（3H，m），7．48－7．53（2H，m），7．56（1H，dd，J＝9Hz，2Hz），7．65（1H，ddd，J＝8Hz，7Hz，1Hz），7．88（1H，d，J＝2Hz），7．90－7．96（1H，m），8．03（1H，dd，J＝8Hz，1Hz），8．54（1H，dd，J＝8Hz，1Hz），11．93（1H，s）

IR（ν，cm^{-1}，KBr）：3404，2208，1664，1528，1214，756

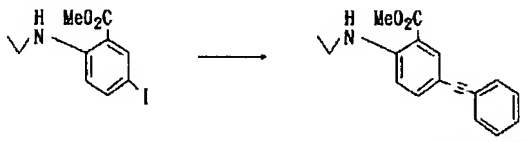
EI－MS（m／z，%）：370（m+，100），352（48），323（7），233（62）

融点205－206℃

【0329】参考例34：2－エチルアミノ－5－フェニルエチニル安息香酸メチル

【0330】

【化80】



【0331】2－エチルアミノ－5－ヨード安息香酸メチル2．24g（7．86mmol）のジエチルアミン（25ml）溶液にエチニルベンゼン1．0ml（9．

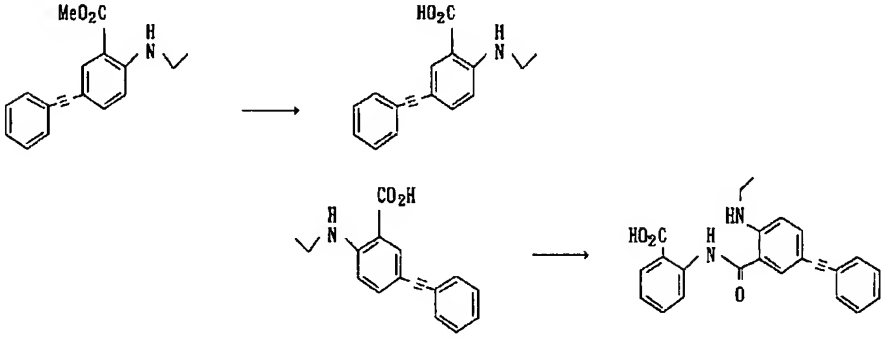
43mmol）、ジクロロビストリフェニルホスフィンパラジウム55mg（0．08mmol）及びヨウ化銅30mg（0．16mmol）を加え、室温で24時間撹拌した後、ジエチルアミンを減圧下留去した。残留物に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物1．26g（収率57．4%）を得た。

【0332】NMR（$CDCl_3$）δ：1．33（3H，t，J=7Hz），3．26（2H，ddd，J=14Hz，7Hz，5Hz），6．65（1H，d，J=9Hz），7．28－7．35（3H，m），7．46－7．52（3H，m），7．80－7．86（1H，m），8．11（1H，d，J=2Hz）

【0333】参考例35：2－エチルアミノ－5－フェニルエチニル安息香酸

【0334】

【化81】



【0335】参考例34で製造した2－エチルアミノ－5－フェニルエチニル安息香酸メチル1．26g（4．51mmol）のエタノール（20ml）溶液に1M－水酸化ナトリウム水溶液10mlを加え、3時間加熱還流した後、エタノールを減圧下留去した。残留物に2M－塩酸水溶液を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物0．96g（収率80．2%）を得た。

【0336】NMR（$DMSO-d_6$）δ：1．22（3H，t，J=7Hz），3．25（2H，q，J=7Hz），6．77（1H，d，J=9Hz），7．36－7．43（3H，m），7．48－7．55（3H，m），7．94（1H，d，J=2Hz）

【0337】実施例44：2－（2－エチルアミノ－5－フェニルエチニルベンズアミド）安息香酸

【0338】

【化82】

【0339】参考例35で製造した2－エチルアミノ－5－フェニルエチニル安息香酸400mg（1．51mmol）の無水ベンゼン溶液（15ml）に窒素雰囲気下塩化チオニル0．13ml（1．81mmol）を加え、1時間加熱還流した後、溶媒を減圧下留去した。残留物の無水トルエン（20ml）溶液に、2－アミノ安息香酸0．25g（1．51mmol）及び炭酸カリウム0．21g（1．81mmol）を加え、窒素雰囲気下7時間加熱還流した後、室温まで冷却した。反応溶液に水を加えた後、有機層を分離し、水層を酢酸エチルにて抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物0．25g（収率60．4%）を得た。

【0340】NMR（$DMSO-d_6$）δ：1．23（3H，t，J=7Hz），3．20－3．26（2H，m），6．83（1H，d，J=9Hz），7．18－7．24（1H，m），7．37－7．46（3H，m），7．48－7．56（3H，m），7．62－7．68（1H，m），7．89（1H，d，J=2Hz），7．93－8．00（1H，m），8．03（1H，dd，J=8Hz，1Hz），8．52（1H，dd，J=8Hz，1Hz），11．95（1H，s）IR（ν，cm^{-1}，KBr）：3328，2972，2212，1654，1534，1252，1222，756

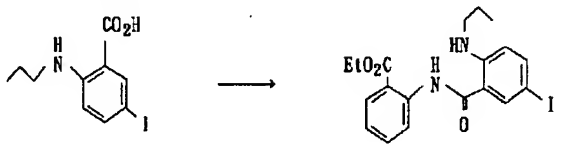
EI－MS（m／z，%）：384（m+，100），366（92），337（22），323（27），247（44），232（25）

融点：202－204℃

【0341】参考例36：2－（2－プロピルアミノ－5－ヨードベンズアミド）安息香酸エチル

【0342】

【化83】



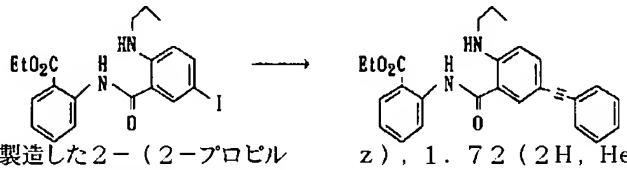
【0343】2－プロピルアミノ－5－ヨード安息香酸1．2g（3．93mmol）の無水ベンゼン溶液（20ml）に窒素雰囲気下塩化チオニル0．34ml（4．72mmol）を加え、1時間加熱還流した後、溶媒を減圧下留去した。残留物の無水トルエン（30ml）溶液に、2－アミノ安息香酸エチル0．7ml（4．72mmol）及び炭酸カリウム0．65g（4．72mmol）を加え、窒素雰囲気下7時間加熱還流した後、室温まで冷却した。反応溶液に水を加えた後、有機層を分離し、水層を酢酸エチルにて抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンにて再結晶し、標記化合物1．0g（収率56．3%）を得た。

【0344】NMR（$CDCl_3$）δ：1．02（3H，t，J＝7Hz），1．45（3H，t，J＝7Hz），1．70（2H，hex，J＝7Hz），3．12（2H，dt，J＝7，5Hz），4．44（2H，q，J＝7Hz），6．50（1H，d，J＝9Hz），7．11（1H，ddd，J＝8Hz，7Hz，1Hz），7．52－7．60（2H，m），7．75－7．84（1H，m），7．96（1H，d，J＝2Hz），8．09（1H，dd，J＝8Hz，1Hz），8．67（1H，dd，J＝8Hz，1Hz），11．74（1H，s）

【0345】参考例37：2－（2－プロピルアミノ－5－フェニルエチニルベンズアミド）安息香酸エチル

【0346】

【化84】



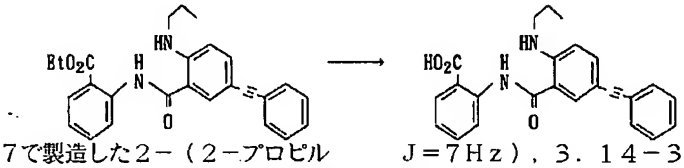
【0347】参考例36で製造した2－（2－プロピルアミノ－5－ヨードベンズアミド）安息香酸エチル500mg（1．10mmol）のジエチルアミン（10ml）溶液にエチニルベンゼン0．16ml（1．78mmol）、ジクロロビストリフェニルホスフィンパラジウム10mg（0．01mmol）及びヨウ化銅6mg（0．02mmol）を加え、室温で20時間撹拌した後、ジエチルアミンを減圧下留去した。残留物に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンにて再結晶し、標記化合物0．38g（収率81．8%）を得た。

【0348】NMR（$CDCl_3$）δ：1．04（3H，t，J＝7Hz），1．43（3H，t，J＝7Hz），1．72（2H，Hex，J＝7Hz），3．18（2H，dt，J＝7，5Hz），4．43（2H，q，J＝7Hz），6．69（1H，d，J＝9Hz），7．12（1H，dddJ＝8Hz，7Hz，1Hz），7．28－7．36（3H，m），7．47－7．53（3H，m），7．58（1H，ddd，J＝8Hz，7Hz，1Hz），7．92（1H，d，J＝2Hz），8．00－8．06（1H，m），8．10（1H，dd，J＝8Hz，1Hz），8．68（1H，dd，J＝8Hz，1Hz），11．77（1H，s）

【0349】実施例45：2－（2－プロピルアミノ－5－フェニルエチニルベンズアミド）安息香酸

【0350】

【化85】



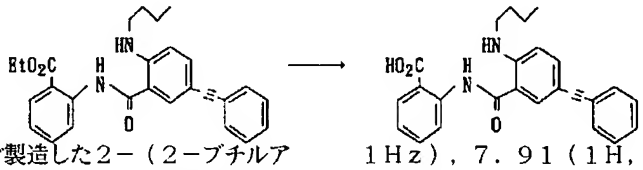
【0351】参考例37で製造した2－（2－プロピルアミノ－5－フェニルエチニルベンズアミド）安息香酸エチル380mg（0．89mmol）のジオキサン（20ml）溶液に1M－水酸化ナトリウム水溶液10mlを加え、4時間加熱還流した。反応溶液に2M－塩酸を加え、酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチルーヘキサンにて再結晶し、標記化合物250mg（収率70．5%）を得た。

【0352】NMR（DMSO－d_6）δ：0．98（3H，t，J＝7Hz），1．63（2H，hex，J＝7Hz），3．14－3．24（2H，m），6．83（1H，d，J＝9Hz），7．18－7．25（1H，m），7．38－7．45（3H，m），7．48－7．56（3H，m），7．60－7．68（1H，m），7．90（1H，d，J＝2Hz），8．03（1H，dd，J＝8Hz，1Hz），8．07－8．12（1H，m），8．52（1H，d，J＝8Hz），11．95（1H，s）

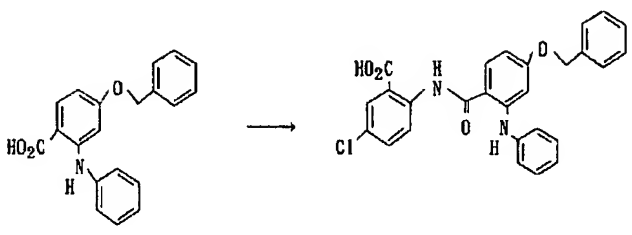
IR（ν，cm^{-1}，KBr）：3324，2212，1658，1532，1254，1220，756

EI－MS（m／z，%）：398（m+，100），380（35），351（27），323（7），23

2（58）
融点：193－194℃
【0353】参考例38：2－（2－ブチルアミノ－5－ヨードベンズアミド）安息香酸エチル500mg（1.07mmol）のジエチルアミン（10ml）溶液にエチニルベンゼン0.16ml（1.78mmol）、ジクロロビストリフェニルホスフィンパラジウム10mg（0.01mmol）及びヨウ化銅6mg（0.02mmol）を加え、室温で19時間撹拌した後、ジエチルアミンを減圧下留去した。残留物に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物0.38g（収率80.6%）を得た。
【0356】NMR（$CDCl_3$）δ：0.97（3H，t，J＝7Hz），1.43（3H，t，J＝7Hz），1.43－1.52（2H，m），1.64－1.74（2H，m），3.18－3.26（2H，m），4.42（2H，q，J＝7Hz），6.69（1H，d，J＝9Hz），7.09－7.14（1H，m），7.26－7.36（3H，m），7.47－7.54（3H，m），7.54－7.62（1H，m），7.91（1H，d，J＝2Hz），7.97－8.04（1H，m），8.10（1H，dd，J＝8Hz，1Hz），8.68（1H，dd，J＝8Hz，1Hz），11.76（1H，s）
【0357】実施例46：2－（2－ブチルアミノ－5－フェニルエチニルベンズアミド）安息香酸
【0358】
【化87】



【0359】参考例38で製造した2－（2－ブチルアミノ－5－フェニルエチニルベンズアミド）安息香酸エチル380mg（0.86mmol）のジオキサン（20ml）溶液に1M－水酸化ナトリウム水溶液10mlを加え、6時間加熱還流した。反応溶液に2M－塩酸を加え、酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物294mg（収率82.7%）を得た。
【0360】NMR（$CDCl_3$）δ：0.98（3H，t，J＝7Hz），1.48（2H，hex，J＝7Hz），1.6－1.74（2H，m），3.22（2H，t，J＝7Hz），6.71（1H，d，J＝9Hz），6.93－6.98（1H，m），7.23－7.30（2H，m），7.48－7.54（3H，m），7.60（1H，ddd，J＝8Hz，7Hz，1Hz），7.91（1H，d，J＝2Hz），8.00（1H，dd，J＝8Hz，1Hz），8.78（1H，dd，J＝8Hz，1Hz），11.68（1H，s）
IR（ν，cm^{-1}，KBr）：3368，3320，2964，2216，1652，1528，1252，1218，756
EI－MS（m／z，%）：412（m+，100），394（26），351（22），323（7），232（71）
融点：188－189℃
【0361】実施例47：5－クロロ－2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）安息香酸
【0362】
【化88】



【0363】4－ベンジルオキシ－2－フェニルアミノ安息香酸0．50g（1．56mmol）の塩化メチレン（10ml）溶液に、窒素雰囲気下塩化チオニルを0．28g（2．35mmol）加え、氷冷下2時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（10ml）溶液を2－アミノ－5－クロロ安息香酸0．40g（2．35mmol）及びトリエチルアミン0．65ml（2．35mmol）の塩化メチレン（15ml）溶液に滴下し、室温で17時間撹拌した。反応溶液に水を加え、塩化メチレンで抽出した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィー及びアセトニトリルからの再結晶で精製し、標記化合物390mg（収率53．0%）を得た。

【0364】NMR（DMSO－d_6）δ：5．14（2H，s），6．62（1H，dd，J＝9Hz，2Hz），6．80（1H，d，J＝2Hz），7．02（1H，t，J＝7Hz），7．12（2H，d，J＝7Hz），7．25－7．41（7H，m），7．69（1H，dd，J＝9Hz，2Hz），7．74（1H，d，J＝9Hz），7．96（1H，d，J＝2Hz），8．59（1H，d，J＝9Hz），9．70（1H，s），11．87（1H，s）

IR（ν，cm^{-1}，KBr）：1652，1582，1434，1256，752

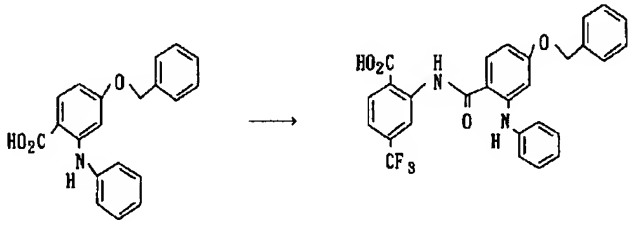
EI－MS（m／z，%）：472（m+，6），386（15），329（13），301（7），251（10），119（10），91（100）

融点：229－230℃

【0365】実施例48：2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）－4－トリフルオロメチル安息香酸

【0366】

【化89】



【0367】4－ベンジルオキシ－2－フェニルアミノ安息香酸500mg（1．56mmol）の塩化メチレン（15ml）溶液に、塩化チオニルを186mg（1．56mmol）加え、氷冷下2時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（10ml）溶液を2－アミノ－4－トリフルオロメチル安息香酸480mg（2．35mmol）及び炭酸カリウム539mg（3．9mmol）の塩化メチレン（15ml）懸濁溶液に滴下し、1時間撹拌後、トリエチルアミン1ml（2．35mmol）を加え、さらに室温で15時間撹拌した。反応溶液に1M－塩酸を加え、有機層を塩化メチレンで抽出した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥した後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィー及びアセトニトリルからの再結晶で精製し、標記化合物370mg（収率46．5%）を得た。

【0368】NMR（DMSO－d_6）δ：5．13（2H，s），6．64（1H，dd，J＝9Hz，2Hz），6．79（1H，d，J＝2Hz），7．03（1H，t，J＝7Hz），7．14（2H，dd，J＝8Hz，1Hz），7．27－7．44（7H，m），7．53（1H，dd，J＝8Hz，1Hz），7．76（1H，d，J＝9Hz），8．21（1H，d，J＝8Hz），8．95（1H，d，J＝1Hz），9．60（1H，s），12．00（1H，s）

IR（ν，cm^{-1}，KBr）：1645，1597，1573，1521，1233，749

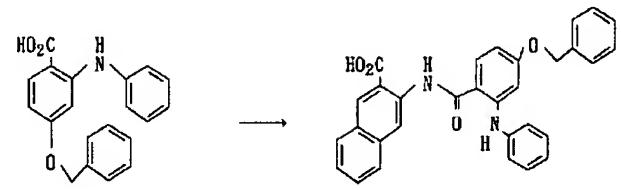
EI－MS（m／z，%）：506（m+，53），488（9），446（4），329（5），302（17），301（39），300（16），272（9），211（7），91（100）

融点：207－208℃

【0369】実施例49：3－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）－2－ナフタレンカルボン酸

【0370】

【化90】



【0371】4－ベンジルオキシ－2－フェニルアミノ安息香酸500mg（1．56mmol）の塩化メチレン（10ml）溶液に、氷冷下塩化チオニル186mg（1．56mmol）を加え、2時間撹拌した。この溶液を3－アミノ－2ナフタレンカルボン酸438mg（2．34mmol）及び，トリエチルアミン1．09ml（7．83mmol）の塩化メチレン（15ml）溶液に滴下し、室温で三日間撹拌した。反応溶液を1M－塩酸で酸性にし、酢酸エチルで抽出した。水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をエタノールから再結晶し、標記化合物438mg（収率57．0%）を得た。

【0372】NMR（DMSO－d_6）δ：5．15（2H，s），6．64（1H，dd，J＝9Hz，2Hz），6．83（1H，d，J＝2Hz），7．03（1H，t，J＝7Hz），7．15（2H，d，J＝8Hz），7．29－7．42（7H，m），7．50（1H，t，J＝7Hz），7．63（1H，t，J＝8Hz），7．81（1H，d，J＝9Hz），7．94（1H，d，J＝8Hz），8．05（1H，d，J＝8Hz），8．74（1H，s），9．04（1H，s），9．87（1H，s），12．06（1H，s）

IR（ν，cm^{-1}，KBr）：3352，1694，1642，1546，1254，740

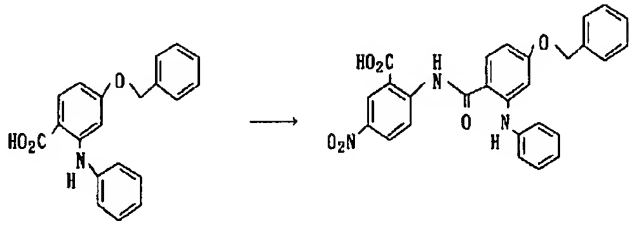
EI－MS（m／z，%）：488（m+，5），446（9），386（6），330（5），329（10），328（5），251（11），129（9），121（9），119（10），97（8），91（72）

融点：268℃

【0373】実施例50：2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）－5－ニトロ安息香酸

【0374】

【化91】



【0375】4－ベンジルオキシ－2－フェニルアミノ安息香酸580mg（1．82mmol）の塩化メチレン（10ml）溶液に、氷冷下塩化チオニルを324mg（2．72mmol）加え、氷冷で2時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（10ml）溶液を2－アミノ－5－ニトロ安息香酸365mg（2．00mmol）及び，トリエチルアミン0．76ml（5．46mmol）の塩化メチレン（10ml）溶液に滴下し、室温で20時間撹拌した。反応溶液に水を加え塩化メチレンで抽出した。1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィー及びアセトニトリルからの再結晶で精製し、標記化合物440mg（収率50．0%）を得た。

【0376】NMR（DMSO－d_6）δ：5．04（2H，s），6．51（1H，dd，J＝9Hz，2Hz），6．82（1H，d，J＝2Hz），7．10（1H，dd，J＝7Hz，7Hz），7．17（2H，dd，J＝8Hz，1Hz），7．30－7．41（7H，m），8．45（1H，dd，J＝9Hz，2Hz），7．72（1H，d，J＝9Hz），9．00－9．10（2H，s），9．91（1H，s），11．99（1H，s）

IR（ν，cm^{-1}，KBr）：1694，1658，1550，1228，756，744

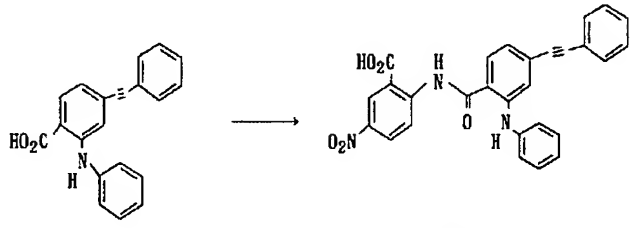
FAB－MS（m／z，%）：484（M－H，3），302（100）

融点：202－203℃

【0377】実施例51：5－ニトロ－2－（2－フェニルアミノ4－フェニルエチニルベンズアミド）安息香酸

【0378】

【化92】



【0379】2－フェニルアミノ－4－フェニルエチニル安息香酸200mg（0．64mmol）の塩化メチ

レン（10ml）溶液に、氷冷下塩化チオニルを114mg（0．96mmol）加え、氷冷で2時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（10ml）溶液を2－アミノ－5－ニトロ安息香酸174mg（0．96mmol）及び，トリエチルアミン0．26ml（1．91mmol）の塩化メチレン（10ml）溶液に滴下し、室温で20時間撹拌した。反応溶液に水を加え塩化メチレンで抽出した。1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィー及びアセトニトリルからの再結晶で精製し、標記化合物を92mg（収率30．0%）を得た。

【0380】NMR（DMSO－d_6）δ：．07（1H，t，J＝7Hz），7　．13（1H，dd，J＝8Hz，1Hz），7．23（2H，d，J＝7Hz），7．34－7．59（8H，m），7．83（1H，d，J＝8Hz），8．49（1H，dd，J＝9Hz，3Hz），8．76（1H，d，J＝3Hz），8．84（1H，d，J＝9Hz），9．27（1H，s），12．48（1H，s）

IR（ν，cm^{-1}，KBr）：2212，1704，1636，1596，1514，1220，762

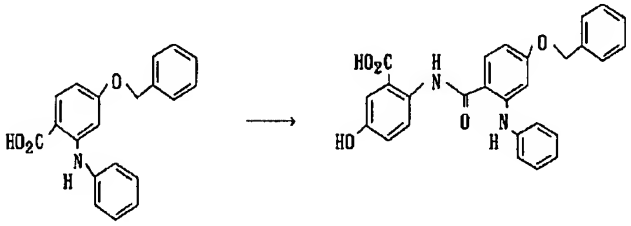
FAB－MS（m／z，%）：476（M－H，100）

融点：248－250℃

【0381】実施例52：2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）－5－ヒドロキシ安息香酸

【0382】

【化93】



【0383】4－ベンジルオキシ－2－フェニルアミノ安息香酸500mg（1．56mmol）の塩化メチレン（10ml）溶液に、塩化チオニル0．15ml（2．00mmol）加え、室温で1時間撹拌した後、溶媒を減圧下留去した。残留物のトルエン（20ml）溶液に、2－アミノ－5－ヒドロキシ安息香酸240mg（1．56mmol）及び炭酸カリウム330mg（2．39mmol）を加え、20時間加熱還流した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィー及びアセトニトリルからの再結晶で精製し、標記化合物243mg（収率34．0%）を得た。

【0384】NMR（DMSO－d_6）δ：5．13（2H，s），6．59（1H，dd，J＝9Hz，2Hz），6．80（1H，d，J＝2Hz），6．98－7．04（2H，m），7．11（2H，d，J＝8Hz），7．25－7．43（8H，m），7．72（1H，d，J＝9Hz），8．31（1H，d，J＝9Hz），9．61（1H，s），9．83（1H，s），11．62（1H，m）

IR（ν，cm^{-1}，KBr）：3364，1668，1644，1614，1588，1546，1524，1498，1472，1288，1252，1226，1192，762，740

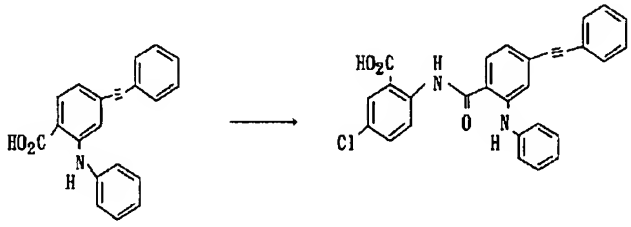
FAB－MS（m／z，%）：453（M－H，100）

融点212－214℃

【0385】実施例53：5－クロロ－2－（2－フェニルアミノ4－フェニルエチニルベンズアミド）安息香酸

【0386】

【化94】



【0387】2－フェニルアミノ－4－フェニルエチニル安息香酸250mg（0．80mmol）の塩化メチレン（15ml）溶液に、塩化チオニルを0．07ml（0．96mmol）加え、1．5時間室温で撹拌した後、溶媒を減圧下留去した。残留物のトルエン（20ml）溶液に、2－アミノ－5－クロロ安息香酸171mg（1．0mmol）及び炭酸カリウム276mg（2．0mmol）を加え、20時間加熱還流した。反

応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルから再結晶し、標記化合物300mg（収率80．0%）得た。

【0388】NMR（DMSO－d_6）δ：7．06（1H，t，J＝7Hz），7．11（1H，dd，J＝8Hz，1Hz），7．22（2H，d，J＝7Hz），7．33－7．39（3H，m），7．41－7．46（3H，m），7．54－7．59（2H，m），7．71（1H，dd，J＝9Hz，2Hz），7．80（1H，d，J＝8Hz），7．97（1H，d，J＝2Hz），8．57（1H，d，J＝9Hz），9．30（1H，s），12．00（1H，s）

IR（ν，cm^{-1}，KBr）：3384，3208，1704，1636，1608，1580，1550，1518，1496，1286，1222，1222，1188，750，692

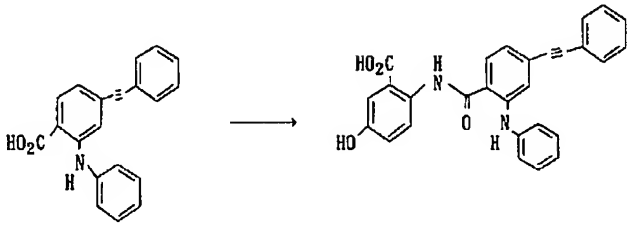
EI－MS（m／z，%）：466（m+，4），296（6），295（10），91（100）

融点：256－257℃

【0389】実施例54：5－ヒドロキシ－2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0390】

【化95】



【0391】2－フェニルアミノ－4－フェニルエチニル安息香酸500mg（1．60mmol）の塩化メチレン（20ml）溶液に、塩化チオニルを0．15ml（2．00mmol）加え、室温で1時間撹拌した後、溶媒を減圧下留去した。残留物のトルエン（50ml）溶液に、2－アミノ－5－ヒドロキシ安息香酸294mg（1．92mmol）及び炭酸カリウム266mg（1．92mmol）を加え、20時間加熱還流した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルから再結晶し、標記化合物500mg（収率70．0%）を得た。

【0392】NMR（DMSO－d_6）δ：7．03－7．13（3H，m），7．23（2H，dd，J＝8Hz，1Hz），7．34－7．45（7H，m），7．54－7．59（2H，m），7．79（1H，d，J＝8Hz），8．29（1H，d，J＝9Hz），9．41（1H，s），9．68（1H，s），11．58（1H，s），13．58（1H，m）

IR（ν，cm^{-1}，KBr）：3344，3048，1680，1648，1588，1534，1498，1416，1290，1254，1220，754

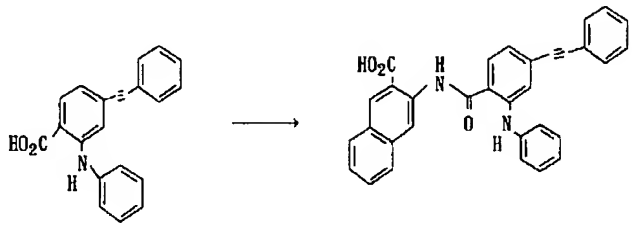
FAB－MS（m／z，%）：447（M－H，100）

融点：233－234℃

【0393】実施例55：3－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）－2－ナフタレンカルボン酸

【0394】

【化96】



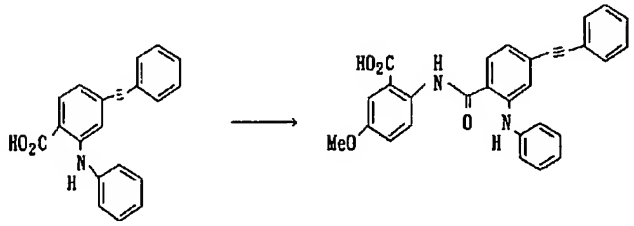
【0395】2－フェニルアミノ－4－フェニルエチニル安息香酸500mg（1．60mmol）の塩化メチレン（25ml）溶液に、塩化チオニルを0．4ml（1．92mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物のトルエン（50ml）溶液に、3－アミノ－2－ナフタレンカルボン酸450mg（1．92mmol）及び炭酸カリウム265mg（1．92mmol）を加え、20時間加熱還流した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィー及びメタノール洗浄により精製し、標記化合物を286mg（収率37．0%）を得た。

【0396】NMR（DMSO－d_6）δ：7．07（1H，t，J＝7Hz），7．14（1H，dd，J＝8Hz，1Hz），7．25－7．29（2H，m），7．35－7．46（6H，m），7．50－7．60（4H，m），7．62－7．68（1H，m），7．87（1H，d，J＝8Hz），7．94（1H，d，J＝8Hz），8．07（1H，d，J＝8Hz），8．75（1H，s），9．04（1H，s），9．47（1H，s），12．11（1H，s），13．6－14．4（1H，m）
IR（ν，cm^{-1}，KBr）：3360，3132，3056，1698，1638，1548，1276，1262，1194，754，692
EI－MS（m／z，%）：482（m+，17），464（6），446（15），295（32），278（13），91（100）
融点：264℃（dec．）

【0397】実施例56：5－メトキシ－2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0398】

【化97】



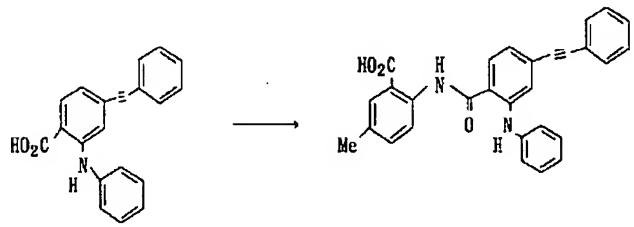
【0399】2－フェニルアミノ－4－フェニルエチニル安息香酸500mg（1．60mmol）の塩化メチレン（25ml）溶液に、塩化チオニルを0．14ml（1．92mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物のトルエン（50ml）溶液に、2－アミノ－5－メトキシ安息香酸379mg（2．27mmol）及び炭酸カリウム265mg（1．92mmol）を加え、20時間加熱還流した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルから再結晶し、標記化合物436mg（収率59．0%）を得た。

【0400】NMR（DMSO－d_6）δ：7．06（1H，t，J＝7Hz），7．10（1H，dd，J＝8Hz，1Hz），7．21－7．28（3H，m），7．33－7．39（3H，m），7．41－7．46（3H，m），7．50（1H，d，J＝3Hz），7．54－7．59（2H，m），7．80（1H，d，J＝8Hz），8．40（1H，d，J＝9Hz），9．39（1H，s），11．66（1H，s）
IR（ν，cm^{-1}，KBr）：3348，1700，1684，1636，1610，1598，1536，1496，1416，1324，1286，1222，1176，1042，830，750
EI－MS（m／z，%）：462（m+，84），444（26），426（7），296（90），295（100），267（14），167（34）
融点：234－235℃

【0401】実施例57：5－メチル－2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0402】

【化98】



【0403】2－フェニルアミノ－4－フェニルエチニル安息香酸300mg（0．96mmol）の塩化メチレン（20ml）溶液に、塩化チオニルを0．08ml（1．1mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物のトルエン（50ml）溶液に、2－アミノ－5－メチル安息香酸174mg（1．15mmol）及び炭酸カリウム159mg（1．15mmol）を加え、20時間加熱還流した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルから再結晶し、標記化合物375mg（収率88．0%）得た。

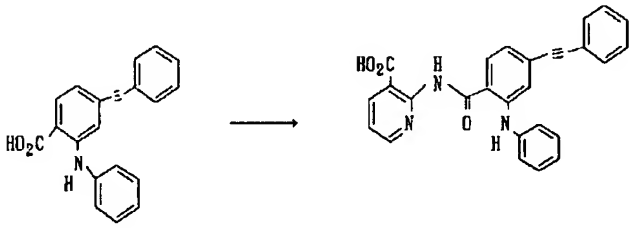
【0404】NMR（DMSO－d_6）δ：2．33（3H，s），7．06（1H，t，J＝7Hz），7．10（1H，dd，J＝8Hz，1Hz），7．2

4（2H，dd，J＝8Hz，1Hz），7．33－7．45（6H，m），7．47（1H，dd，J＝8Hz，1Hz），7．54－7．60（2H，m）7．80（1H，d，J＝8Hz），7．85（1H，d，J＝2Hz），8．46（1H，d，J＝8Hz），9．39（1H，s），11．95（1H，s）13．5－13．9（1H，m）
IR（ν，cm^{-1}，KBr）：3228，2212，1698，1640，1596，1582，1536，1496，1416，1322，1290，1256，1224，1176，1060，750
EI－MS（m／z，%）：446（m+，7），428（2），295（10），267（2）
融点：248－250℃

【0405】実施例58：2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）ニコチン酸

【0406】

【化99】



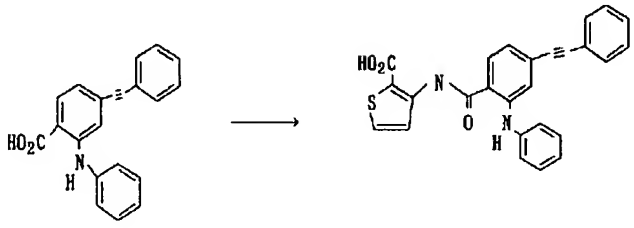
【0407】2－フェニルアミノ－4－フェニルエチニル安息香酸300mg（0．96mmol）の塩化メチレン（20ml）溶液に、塩化チオニルを0．08ml（1．1mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、2－アミノニコチン酸145mg（1．05mmol）及びトリエチルアミン1mlを加え、室温で20時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルから再結晶し、標記化合物124mg（収率30．0%）得た。

【0408】NMR（DMSO－d_6）δ：7．04－7．10（2H，m），7．21－7．25（2H，m），7．32－7．46（7H，m）7．55－7．60（2H，m），7．88（1H，d，J＝8Hz），8．26（1H，dd，J＝8Hz，1Hz），8．59（1H，dd，J＝5，2Hz），9．20－9．40（1H，m），11．40－11．60（1H，m）
IR（ν，cm^{-1}，KBr）：3444，3256，3100－2900，2212，1756，1664，1640，1594，1554，1518，1496，1444，1412，1316，1272，1258，1244，1210，770，752
FAB－MS（m／z，%）：434（M+H，17），296（100）
融点：236－237℃

【0409】実施例59：3－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）チオフェンカルボン酸

【0410】

【化100】



【0411】2－フェニルアミノ－4－フェニルエチニル安息香酸250mg（0．8mmol）の塩化メチレン（15ml）溶液に、塩化チオニルを0．08ml（1．0mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、3－アミノ－2－チオフェンカルボン酸メチル151mg（0．96mmol）及び炭酸カリウム133mg（0．96mmol）を加え、室温で20時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製した。得られたエステル体をエタノール（25ml）に溶解し、1M－水酸化ナトリウム水溶液1．4mlを加え、4時間加熱還流した後、エタノールを減圧下留去した。残留物を塩酸で酸性にした後、沈殿物を沪過し、アセトニトリルから再結晶して標記化合物236mg（収率78．0%）得た。

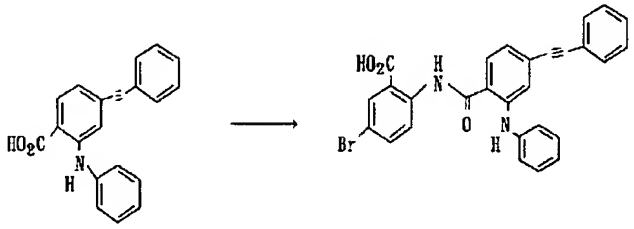
【0412】NMR（DMSO－d_6）δ：7．05（1H，t，J＝7Hz），7．15（1H，dd，J

＝8Hz，1Hz），7．20（2H，dd，J＝8Hz，1Hz），7．32－7．46（6H，m），7．55－7．60（2H，m），7．79（1H，d，J＝8Hz），7．90（1H，d，J＝5Hz），8．08（1H，d，J＝5Hz），9．20（1H，s），11．36（1H，s），13．5－13．7（1H，m）
IR（ν，cm^{-1}，KBr）：3392，3260，3044，2636，2212，1640，1608，1554，1498，1446，1408，1368，1258，1242，1214，756
EI－MS（m／z，%）：420（m+，41），296（100），278（75），256（38），205（55），178（46），147（46），133（54），129（62），121（58），119（48），115（50），108（70），105（69）
融点：218－220℃

【0413】実施例60：5－ブロモ－2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸

【0414】

【化101】



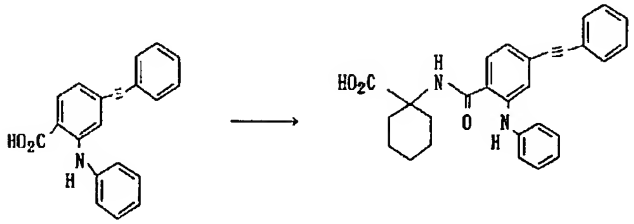
【0415】2－フェニルアミノ－4－フェニルエチニル安息香酸500mg（1．60mmol）の塩化メチレン（20ml）溶液に、塩化チオニルを0．15ml（2．00mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、2－アミノ－5－ブロモ安息香酸415mg（1．92mmol）及び炭酸カリウム266mg（1．92mmol）を加え、室温で20時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルから再結晶し、標記化合物455mg（収率55．6%）得た。

【0416】NMR（DMSO－d_6）δ：7．06（1H，t，J＝7Hz），7．10（1H，dd，J＝8Hz，1，Hz），7．23（2H，dd，J＝8Hz，1Hz），7．33－7．48（6H，m），7．54－7．60（2H，m），7．80（1H，d，J＝8Hz），7．84（1H，dd，J＝9Hz，2Hz）8．09（1H，d，J＝2Hz），8．52（1H，d，J＝9Hz），9．30（1H，s），11．96（1H，s）
IR（ν，cm^{-1}，KBr）：3220，2220，1700，1688，1636，1606，1596，1576，1516，1496，1418，1370，1322，1284，1250，1220，1180，824，790，764，750
EI－MS（m／z，%）：512（m+，10），494（4），295（30），267（7），239（1），190（1），163（1），91（2）
融点261－263℃

【0417】実施例61：1－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）シクロヘキサンカルボン酸

【0418】

【化102】



【0419】2－フェニルアミノ－4－フェニルエチニル安息香酸500mg（1．6mmol）の塩化メチレン（20ml）溶液に、塩化チオニルを0．15ml（2mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、1，1－アミノシクロヘキサンカルボン酸ベンジル448mg（1．92mmol）及び炭酸カリウム266mg（1．92mmol）を加え、室温で20時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルで洗浄

した。得られた結晶をエタノール（10ml）に溶解し、1M－水酸化ナトリウム水溶液2mlを加え、5時間加熱還流した後、エタノールを減圧下留去した。残留物を塩酸で酸性にした後、沈殿物を沪過し、エーテルから再結晶し、標記化合物434mg（収率62.0%）得た。

【0420】NMR（DMSO－d_6）δ：1.22－1.35（1H, m），1.43－1.62（5H, m），1.68－1.82（2H, m），2.03－2.18（2H, m），7.01－7.07（2H, m），7.18（2H, dd, J=8Hz, 1Hz），7.31－7.45（6H, m），7.54－7.59（2H, m），7.73（1H, d, J=8Hz, Hz），8.52（1H, s），9.27（1H, s），12.27（1H, s）

IR（ν, cm^{-1}, KBr）：3432, 3396, 3236, 3040, 2932, 2860, 2624, 2208, 1718, 1634, 1590, 1558, 1516, 1496, 1418, 1270, 1172, 868, 782, 758

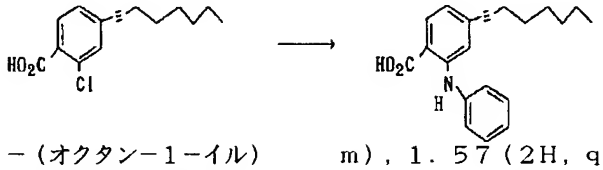
EI－MS（m/z, %）：438（m+, 49），420（8），394（3），349（14），295（100），267（14），239（3），163（3），98（6），81（3）

融点194－195℃

【0421】参考例39：4－（オクタン－1－イル）－2－フェニルアミノ安息香酸

【0422】

【化103】



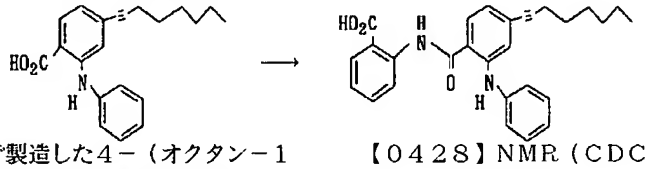
【0423】2－クロロ－4－（オクタン－1－イル）安息香酸1.95g（7.36mmol）のアニリン（20ml）溶液に、炭酸カリウム1.22g（8.83mmol）及び5wt.%の活性化銅を加え、3時間加熱還流し、アニリンを減圧下留去した。残留物を1M－塩酸で酸性にした後、酢酸エチルで抽出した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を塩化メチレンで洗浄し、メタノールから再結晶し、標記化合物2.12g（収率90.0%）を得た。

【0424】NMR（$CDCl_3$）δ：0.89（3H, t, J=7Hz），1.23－1.43（6H, m），1.57（2H, q, J=7Hz）2.37（2H, t, J=7Hz），6.75（1H, dd, J=8Hz, 1Hz），7.15（1H, ddd, J=7Hz, 7Hz, 1Hz），7.21（1H, d, J=1Hz），7.24－7.29（2H, m），7.35－7.42（2H, m），7.93（1H, d, J=8Hz），9.28（1H, s）

【0425】実施例62：2－［4－（オクタン－1－イル）－2－フェニルアミノフェニルアミノベンズアミド］安息香酸

【0426】

【化104】



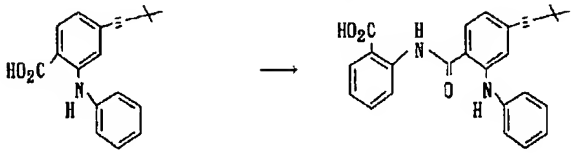
【0427】参考例39で製造した4－（オクタン－1－イル）－2－フェニルアミノ安息香酸520mg（1.62mmol）の塩化メチレン（20ml）溶液に、塩化チオニルを0.12ml（1.62mmol）加え、室温で3時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、2－アミノ安息香酸267mg（1.94mmol）及び炭酸カリウム268mg（1.94mmol）及びトリエチルアミン0.27ml（1.94mmol）を加え、室温で20時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールからの再結晶で精製し、標記化合物450mg（収率63%）を得た。

【0428】NMR（$CDCl_3$）δ：0.88（3H, t, J=7Hz），1.20－1.44（10H, m），1.50－1.60（2H、m）2.38（2H, t, J=7Hz），6.87（1H, dd, J=7, 1Hz），7.07（1H, t, J=7Hz），7.14－7.20（1H, m），7.23－7.30（2H, m），7.32－7.39（3H, m），7.64－7.70（2H, m），8.15－8.21（1H, m），8.83（1H, dd, J=8Hz, 1Hz），9.61（1H, s），11.69（1H, s）

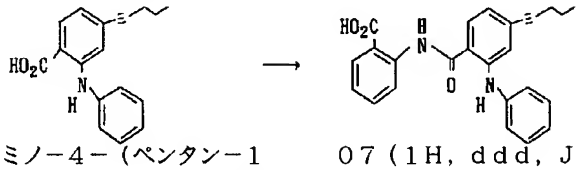
IR（ν, cm^{-1}, KBr）：3300, 3044, 2228, 1682, 1652, 1606, 1580, 1562, 1542, 1516, 1498, 1470, 1452, 1420, 1320, 1294, 1258, 1224, 1160, 1068, 1028, 870, 75

2
EI－MS（m／z，%）：440（m+，100），422（24），303（59），260（20），246（20），233（31），204（23）
融点：165－167℃

【0429】実施例63：2－［4－（3，3－ジメチルブチニル）－2－フェニルアミノベンズアミド］安息香酸
【0430】
【化105】

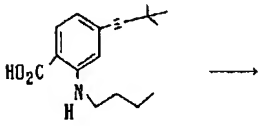


【0431】4－（3，3－ジメチルブチニル）－2－フェニルアミノ安息香酸587mg（2．00mmol）の塩化メチレン（20ml）溶液に、塩化チオニルを0．2ml（2．67mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、2－アミノ安息香酸302mg（2．20mmol）、炭酸カリウム304mg（2．20mmol）及びトリエチルアミン0．30ml（2．20mmol）を加え、室温で18時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルからの再結晶で精製し、標記化合物654mg（収率79．0%）を得た。
【0432】NMR（$CDCl_3$）δ：1．30（9H，s），6．87（1H，dd，J＝8Hz，1Hz），7．04－7．10（1H，m），7．14－7．20（1H，m），7．23－7．29（2H，m），7．32－7．39（3H，m），7．63－7．70（2H，m），8．19（1H，dd，J＝8Hz，1Hz），8．82（1H，dd，J＝8Hz，1Hz），9．60（1H，s），11．67（1H，s）
IR（ν，cm^{-1}，KBr）：3288，2972，2224，1656，1608，1582，1560，1532，1498，1420，1294，1256，1224，1162，900，764，752
EI－MS（m／z，%）：412（m+，44），394（6），295（2），275（76），260（38），246（5）
融点：225－227℃
【0433】実施例64：2－［2－フェニルアミノ－4－（ペンタン－1－イル）ベンズアミド］安息香酸
【0434】
【化106】



【0435】2－フェニルアミノ－4－（ペンタン－1－イル）安息香酸510mg（1．83mmol）の塩化メチレン（25ml）溶液に、塩化チオニルを0．14ml（1．83mmol）加え、室温で1時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、2－アミノ安息香酸302mg（2．20mmol）、炭酸カリウム304mg（2．20mmol）及びトリエチルアミン0．30ml（2．20mmol）を加え、室温で20時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルからの再結晶で精製し、標記化合物530mg（収率73．0%）を得た。
【0436】NMR（$CDCl_3$）δ：1．03（3H，t，J＝7Hz）1．50－1．65（2H，m），2．37（2H，t，J＝7．1Hz），6．88（1H，dd，J＝1．5Hz，8．3Hz），7．07（1H，ddd，J＝7Hz，7Hz，1Hz），7．14－7．21（1H，m），7．23－7．30（2H，m），7．32－7．40（3H，m），7．63－7．71（2H，m），8．19（1H，dd，J＝8Hz，1Hz），8．83（1H，dd，J＝8Hz，1Hz），9．60（1H，s），11．67（1H，s）
IR（ν，cm^{-1}，KBr）：3256，3020，2872，2224，1656，1606，1582，1562，1534，1498，1470，1452，1420，1318，1258，1222，1162，892，758，
EI－MS（m／z，%）：398（m+，45%），380（6），261（54），233（17），204（11），190（2），146（2），119（3）
融点：199－200℃
【0437】実施例65：2－［2－ブチルアミノ－4

－（3，3－ジメチルブチニル）ベンズアミド］安息香酸



【0439】2－ブチルアミノ－4－（3，3－ジメチルブチニル）安息香酸547mg（2．00mmol）の塩化メチレン（15ml）溶液に、塩化チオニルを0．2ml（2．67mmol）加え、室温で1．5時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（50ml）溶液に、2－アミノ安息香酸302mg（2．20mmol）、炭酸カリウム304mg（2．20mmol）及びトリエチルアミン0．30ml（2．20mmol）を加え、室温で16時間撹拌した。反応溶液を1M－塩酸で酸性にした後、有機層を分取した。有機層を1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルからの再結晶で精製し、標記化合物659mg（収率84．0%）を得た。

【0440】NMR（$CDCl_3$）δ：0．97（3H，t，J＝7Hz），1．34（9H，s），1．42－1．53（2H，m），1．65－1．73（2H，m），3．16－3．20（2H，m），6．69（1H，dd，J＝8Hz，2Hz），6．74（1H，d，J＝2Hz），7．14（1H，ddd，J＝8Hz，7Hz，1Hz），7．59（1H，d，J＝8Hz），7．63（1H，ddd，J＝8Hz，7Hz，1Hz），8．17（1H，dd，J＝8Hz，1Hz），8．78（1H，dd，J＝8Hz，1Hz）

IR（ν，cm^{-1}，KBr）：3332，3072，2964，2228，1650，1608，1536，1220，766，754

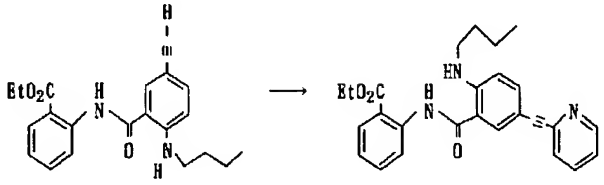
FAB－MS（m／z，%）：391（M－H）

融点：225－227℃

【0441】参考例40：2－［2－ブチルアミノ－5－（2－ピリジルエチニル）ベンズアミド］安息香酸エチル

【0442】

【化108】



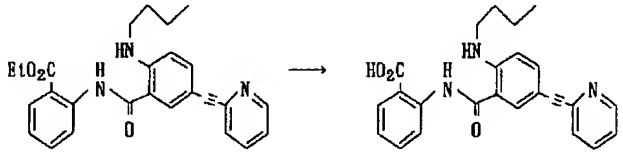
【0443】2－（2－ブチルアミノ－5－エチニルベンズアミド）安息香酸エチル526mg（1．44mmol）のジエチルアミン（10ml）溶液に2－ヨードピリジン0．30ml（2．89mmol）、ジクロロビストリフェニルホスフィンパラジウム16mg（0．01mmol）及びヨウ化銅10mg（0．03mmol）を加え、室温で2時間撹拌した。反応溶液に水を加えた後、酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、水、飽和硫酸水素カリウム水溶液、10%チオ硫酸ナトリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールからの再結晶で精製し、標記化合物375mg（収率77．5%）を得た。

【0444】NMR（$CDCl_3$）δ：0．97（3H，t，J＝7Hz），1．42（3H，t，J＝7Hz），1．40－1．50（2H，m），1．64－1．71（2H，m），3．18－3．24（2H，m），4．43（2H，q，J＝7Hz），7．12（1H，ddd，J＝8Hz，7Hz，1Hz），7．19（1H，ddd，J＝8Hz，5，1Hz），7．50（1H，ddd，J＝8Hz，8Hz，1Hz），7．55－7．61（2H，m），7．66（1H，ddd，J＝8Hz，8Hz，2Hz），7．97（1H，d，J＝2Hz），8．06（1H，t，J＝5Hz），8．10（1H，dd，J＝8Hz，2Hz），8．58－8．61（1H，m），8．66（1H，dd，J＝8Hz，1Hz），11．77（1H，s）

【0445】実施例66：2－［2－ブチルアミノ－5－（2－ピリジルエチニル）ベンズアミド］安息香酸

【0446】

【化109】



【0447】参考例40で製造した2－［2－ブチルアミノ－5－（2－ピリジルエチニル）ベンズアミド］安息香酸エチル375mg（0．85mmol）のエタノール（20ml）溶液に1M－水酸化ナトリウム水溶液1mlを加え、2時間加熱還流した後、室温まで冷却した。反応溶液を飽和硫酸水素カリウムで中和後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールからの再結晶で精製し、標記化合物194mg（収率55．0%）を得た。

【0448】NMR（DMSO－d_6）δ：0．94（3H，t，J＝7Hz），1．36－1．46（2H，m），1．57－1．65（2H，m），3．21－3．26（2H，m），6．86（1H，d，J＝9Hz），7．19－7．24（1H，m），7．37（1H，ddd，J＝8Hz，5，1Hz），7．56－7．60（2H，m），7．65（1H，ddd，J＝8Hz，7Hz，2Hz），7．83（1H，ddd，J＝8Hz，8Hz，2Hz），7．96（1H，d，J＝2Hz），8．04（1H，dd，J＝8Hz，2Hz），8．18（1H，t，J＝5Hz），8．54（1H，dd，J＝8Hz，1Hz），8．57－8．60（1H，m），12．03（1H，s）

IR（ν，cm^{-1}，KBr）：2204，1652，1590，1528，1220，770，756

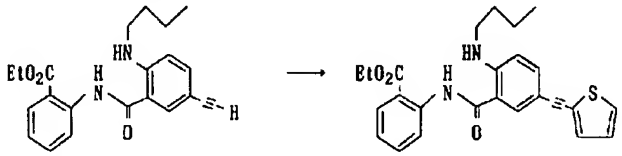
FAB－MS（m／z，%）：412（M－H，100）

融点：179－180℃

【0449】参考例41：2－［2－ブチルアミノ－5－（2－チオフェニルエチニル）ベンズアミド］安息香酸エチル

【0450】

【化110】



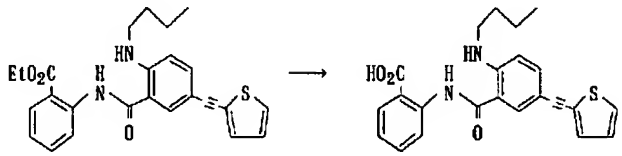
【0451】参考例30で製造した2－（2－ブチルアミノ－5－エチニルベンズアミド）安息香酸エチル500mg（1．37mmol）のジエチルアミン（10ml）溶液に2－ヨードチオフェン0．30ml（2．89mmol）、ジクロロビストリフェニルホスフィンパラジウム16mg（0．01mmol）及びヨウ化銅10mg（0．03mmol）を加え、室温で2時間撹拌した。反応溶液に水を加えた後、酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、水、飽和硫酸水素カリウム水溶液、10%チオ硫酸ナトリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールからの再結晶で精製し、標記化合物233mg（収率38．0%）を得た。

【0452】NMR（$CDCl_3$）δ：0．97（3H，t，J＝7Hz），1．43（3H，t，J＝7Hz），1．41－1．52（2H，m），1．64－1．73（2H，m），3．18－3．22（2H，m），4．43（2H，q，J＝7Hz），6．69（1H，d，J＝9Hz），7．00（1H，dd，J＝5，4Hz），7．12（1H，ddd，J＝8Hz，7Hz，1Hz），7．23－7．26（2H，m），7．47（1H，dd，J＝8Hz，1Hz），7．58（1H，ddd，J＝8Hz，7Hz，1Hz），7．89（1H，J＝2Hz），8．03（1H，t，J＝5Hz），8．10（1H，dd，J＝8Hz，1Hz），8．67（1H，dd，J＝8Hz，1Hz）

【0453】実施例67：2－［2－ブチルアミノ－5－（2－チオフェニルエチニル）ベンズアミド］安息香酸

【0454】

【化111】



【0455】参考例41で製造した2－［2－ブチルアミノ－5－（2－チオフェニルエチニル）ベンズアミド］安息香酸エチル230mg（0．52mmol）のエタノール（20ml）溶液に1M－水酸化ナトリウム水溶液1mlを加え、3時間加熱還流した後、室温まで冷却した。反応溶液を飽和硫酸水素カリウムで中和後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールからの再結晶で精製し、標記化合物185mg（収率85．0%）を得た。

【0456】NMR（DMSO－d_6）δ：0．94（3H，t，J＝7Hz），1．36－1．46（2

H，m），1．56－1．64（2H，m），3．19－3．25（2H，m），6．83（1H，d，J＝9Hz），7．11（1H，dd，J＝5Hz，4Hz），7．18－7．24（1H，m），7．35（1H，dd，J＝4Hz，1Hz）7．52（1H，dd，J＝9Hz，2Hz），7．60－7．67（2H，m），7．88（1H，d，J＝2Hz），8．03（1H，dd，J＝8Hz，1Hz），8．11（1H，dd，J＝8Hz，1Hz），8．51（1H，dd，J＝8Hz，1Hz），11．97（1H，s）

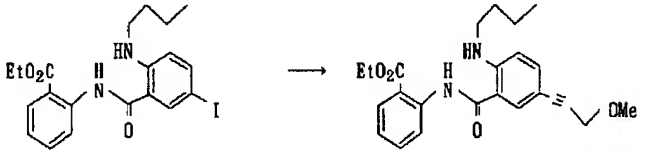
IR（ν，cm^{-1}，KBr）：3320，2964，2208，1652，1602，1530，1254，756

FAB－MS（m／z，％）：417（M－H，16），189（100）融点　79－180℃

【0457】参考例42：2－［2－ブチルアミノ－5－（3－メトキシプロパン－1－イル）ベンズアミド］安息香酸エチル

【0458】

【化112】



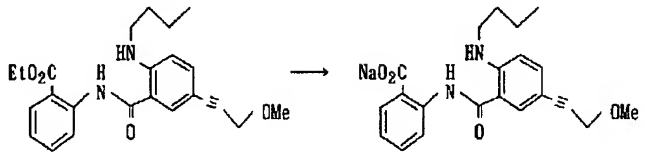
【0459】参考例30で製造した2－（2－ブチルアミノ－5－ヨードベンズアミド）安息香酸エチル700mg（1．50mmol）のジエチルアミン（20ml）及びテトラヒドロフラン（10ml）の混合溶液に3－メトキシ－1－プロピン0．25ml（3．00mmol）、ジクロロビストリフェニルホスフィンパラジウム53mg（0．08mmol）及びヨウ化銅14mg（0．08mmol）を加え、室温で2時間撹拌した。水を加えた後、酢酸エチルで抽出した。有機層を飽和硫酸水素カリウム溶液、10％チオ硫酸ナトリウム水溶液、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールから再結晶で精製し、標記化合物375mg（収率61．2％）を得た。

【0460】NMR（$CDCl_3$）δ：0．96（3H，t，J＝7Hz），1．40－1．51（5H，m），1．62－1．71（2H，m），3．16－3．22（2H，m），3．47（3H，s），4．20（2H，q，J＝7Hz），4．34（2H，s），7．11（1H，ddd，J＝8，7，1Hz），7．41（1H，dd，J＝8Hz，2Hz），7．57（1H，ddd，J＝8，7，1Hz），7．84（1H，d，J＝2Hz），8．00（1H，t，J＝5Hz），8．09（1H，dd，J＝8，1Hz），8．68（1H，dd，J＝8，1Hz），11．75（1H，s）

【0461】実施例68：2－［2－ブチルアミノ－5－（3－メトキシプロパン－1－イル）ベンズアミド］安息香酸ナトリウム塩

【0462】

【化113】



【0463】参考例42で製造した2－［2－ブチルアミノ－5－（3－メトキシプロパン－1－イル）ベンズアミド］安息香酸エチル370mg（0．91mmol）のエタノール（20ml）及びテトラヒドロフラン（20ml）の混合溶液に1M－水酸化ナトリウム水溶液2mlを加え、室温で2時間撹拌した後、溶媒を減圧下留去した。残留物をメタノール－エーテル－ヘキサンからの再結晶で精製し、標記化合物300mg（収率85．9％）を得た。

【0464】NMR（DMSO－d_6）δ：0．93（3H，t，J＝7Hz），1．36－1．46（2H，m），1．55－1．64（2H，m），3．15－3．21（2H，m），4．31（2H，s），6．73（1H，d，J＝9Hz），6．96－7．01（1H，m），7．28－7．33（1H，m），7．39（1H，dd，J＝9Hz，2Hz），7．90（1H，d，J＝2Hz），8．03（1H，dd，J＝8Hz，1Hz），8．37（1H，t，J＝5Hz），8．54（1H，d，J＝8Hz）

IR（ν，cm^{-1}，KBr）：3300，2956，2928，2212，1652，1590，1522，1296，760

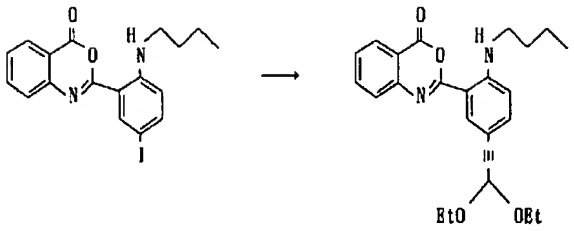
FAB－MS（m／z，％）：424（m＋Na，100）

融点179－180℃

【0465】参考例43：2－［2－ブチルアミノ－5－（3，3－ジエトキシプロパン－1－イル）フェニル］－4－オキソ－4H－3，1－ベンゾキサジン

【0466】

【化114】



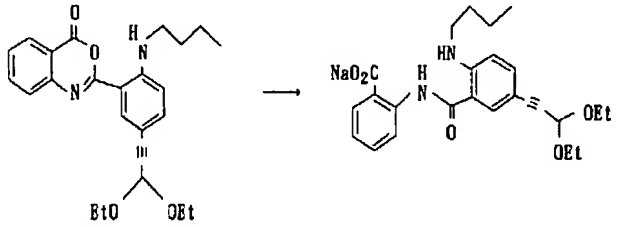
【0467】2－（2－ブチルアミノ－5－ヨードフェニル）－4－オキソ－4H－3，1－ベンゾキサジン1．40g（3．33mmol）のトリエチルアミン（30ml）及びテトラヒドロフラン（15ml）溶液にプロパギルアルデヒドジエチルアセタール0．96ml（1．72mmol）、ジクロロビストリフェニルホスフィンパラジウム30mg（0．03mmol）及びヨウ化銅20mg（0．06mmol）を加え、窒素雰囲気下室温で1時間撹拌した。反応溶液に水を加えた後、酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、水、飽和硫酸水素カリウム水溶液、10％チオ硫酸ナトリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルからの再結晶で精製し、標記化合物625mg（収率41．4％）を得た。

【0468】NMR（$CDCl_3$）δ：1．04（3H，t，J＝7Hz），1．29（6H，t，J＝7Hz），1．53－1．63（2H，m），1．75－1．84（2H，m），3．29－3．34（2H，m），3．63－3．72（2H，m），3．80－3．89（2H，m），5．50（1H，s），6．68（1H，d，J＝9Hz），7．43－7．52（3H，m），7．80（1H，ddd，J＝8Hz，7Hz，1Hz），8．22（1H，ddd，J＝8Hz，1，1Hz），8．32（1H，d，J＝2Hz），9．25（1H，t，J＝5Hz）

【0469】実施例69：2－［2－ブチルアミノ－5－（3，3－ジエトキシプロパン－1－イル）ベンズアミド］安息香酸ナトリウム塩

【0470】

【化115】



【0471】参考例43で製造した2－［2－ブチルアミノ－5－（3，3－ジエトキシプロパン－1－イル）フェニル］－4－オキソ－4H－3，1－ベンゾキサジン600mg（1．43mmol）のエタノール（20ml）及びテトラヒドロフラン（20ml）の混合溶液に1M－水酸化ナトリウム水溶液5mlを加え、室温で2時間撹拌した後、溶媒を減圧下留去した。残留物をメタノール－エーテル－ヘキサンからの再結晶で精製し、標記化合物580mg（収率88．0％）を得た。

【0472】NMR（$CDCl_3$）δ：0．93（3H，t，J＝7Hz），1．18（6H，t，J＝7Hz），1．38－1．46（2H，m），1．55－1．64（2H，m），3．16－3．21（2H，m），3．53－3．61（2H，m），3．65－3．73（2H，m），5．50（1H，s），6．75（1H，d，J＝9Hz），6．98－7．03（1H，m），7．31－7．36（1H，m），7．40（1H，dd，J＝9Hz，2Hz），7．89（1H，d，J＝2Hz），8．06－8．09（1H，m），8．39（1H，t，J＝5Hz），8．55（1H，dd，J＝8Hz，1Hz）

IR（ν，cm^{-1}，KBr）：2960，2932，2220，1660，1594，1520，1288，754

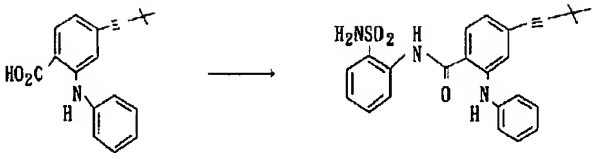
FAB－MS（m／z，％）：437（M－H，34），379（100）

融点：179－180℃

【0473】実施例70：4－（3，3－ジメチルブチニル）－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド

【0474】

【化116】



【0475】4－（3，3－ジメチルブチニル）－2－フェニルアミノ安息香酸1．0g（3．40mmol）及び塩化チオニル0．4mlの塩化メチレン（30ml）溶液を室温で2時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（30ml）溶液を2－アミノベンゼンスルホンアミド0．65g（3．75mmol）のピリジン（50ml）溶液に氷冷下滴下し、18時間室温で撹拌した後、塩化メチレンを減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を1 M－塩酸、水、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物0．8g（収率52．0%）を得た。

【0476】NMR（$CDCl_3$）δ：1．29（9H，s），4．87（2H，br－s），6．85（1H，dd，J＝8Hz，2Hz），7．09（1H，ddd，J＝8Hz，8Hz，1Hz），7．21－7．29（3H，m），7．52－7．59（2H，m），7．57（1H，d，J＝8Hz），7．63（1H，ddd，J＝8Hz，8Hz，1Hz），7．99（1H，dd，J＝8Hz，2Hz），8．41（1H，dd，J＝8Hz，1Hz），9．53（1H，s），10．03（1H，s）

IR（ν，cm^{-1}，KBr）：3364，2972，2928，2224，1642，1586，1556，1516，1500，1472，1442，1420，1334，1290，1272，1222，1154，764

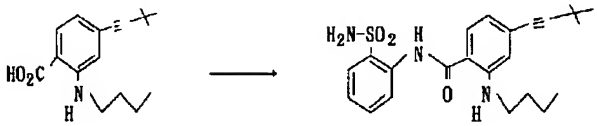
FAB－MS（m／z，%）：446（M－H，100）

融点：101－102℃

【0477】実施例71：2－ブチルアミノ－4－（3，3－ジメチルブチニル）－N－（2－スルファモイルフェニル）ベンズアミド

【0478】

【化117】



【0479】2－ブチルアミノ－4－（3，3－ジメチルブチニル）安息香酸1．0g（3．66mmol）及び塩化チオニル0．4mlの塩化メチレン（30ml）溶液を室温で2時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（30ml）溶液を2－アミノベンゼンスルホンアミド0．7g（4．03mmol）のピリジン（50ml）溶液に氷冷下滴下し、18時間室温で撹拌した後、塩化メチレンを減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を1 M－塩酸、水、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製して、標記化合物0．9g（収率54．0%）を得た。

【0480】NMR（DMSO－d_6）δ：0．97（3H，t，J＝7Hz），1．34（9H，s），1．41－1．51（2H，m），1．62－1．72（2H，m），3．18（2H，t，J＝7Hz），4．83（2H，br－s），6．45（1H，dd，J＝8，2Hz），6．74（1H，d，J＝2Hz），7．23（1H，ddd，J＝8Hz，8Hz，2Hz），7．48（1H，d，J＝8Hz），7．61（1H，ddd，J＝8Hz，8Hz，2Hz），7．86（1H，br－s），7．95（1H，dd，J＝8Hz，2Hz），8．34（1H，dd，J＝8Hz，1Hz），9．70（1H，s）

IR（ν，cm^{-1}，KBr）：3368，3232，3084，2968，2932，2868，2224，1644，1600，1584，1564，1530，1472，1440，1342，1292，1226，1168，1156，896，764

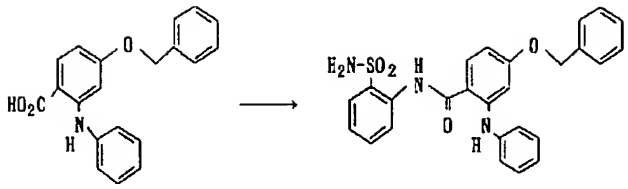
FAB－MS（m／z，%）：426（M－H，100）

融点：130－131℃

【0481】実施例72：4－ベンジルオキシ－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド

【0482】

【化118】



【0483】4－ベンジルオキシ－2－フェニルアミノ安息香酸500mg（1．56mmol）の塩化メチレン（15ml）溶液に、氷冷下塩化チオニルを186mg（1．56mmol）加え、室温で2時間撹拌した。この溶液を2－アミノベンゼンスルホンアミド174mg（0．96mmol）及び、トリエチルアミン1ml（7．8mmol）の塩化メチレン（15ml）溶液に滴下し、室温で4時間撹拌した。反応溶液に、水を加え、酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液、水、1M－塩酸、水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィー及び、エタノールからの再結晶で精製し、標記化合物210mg（収率28．0%）を得た。

【0484】NMR（δ，DMSO－D6）：4．82（2H，s），5．04（2H，s），6．48（1H，dd，J＝9Hz，2Hz），6．85（1H，d，J＝2Hz），7．04－7．10（1H，m），7．15（2H，dd，J＝9Hz，2Hz），7．22－7．41（8H，m），7．60－7．65（2H，m），7．98（1H，dd，J＝8Hz，1Hz），8．38（1H，dd，J＝8Hz，1Hz），9．74（1H，s），9．87（1H，s）

IR（ν，cm^{-1}，KBr）：1646，1580，1522，1286，756

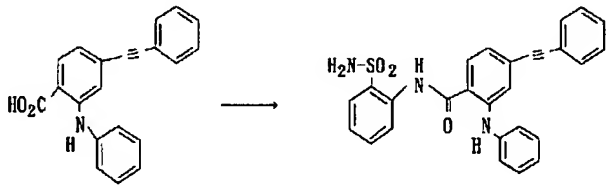
EI－MS（m／z，%）：473（31），446（10），302（18），301（30），300（11），91（100）

融点：171－172℃

【0485】実施例73：4－フェニルエチニル－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド

【0486】

【化119】



【0487】2－フェニルアミノ－4－フェニルエチニル安息香酸1g（3．40mmol）及び塩化チオニル0．4mlの塩化メチレン（30ml）溶液を室温で2時間撹拌した後、溶媒を減圧下留去した。残留物の塩化メチレン（30ml）溶液を2－アミノベンゼンスルホンアミド0．65g（3．75mmol）のピリジン（50ml）溶液に氷冷下滴下し、18時間室温で撹拌した後、塩化メチレンを減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を1M－塩酸、水、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製して、標記化合物0．8g（収率52．0%）を得た。

【0488】NMR（$CDCl_3$）δ：1．29（9H，s），4．87（2H，br－s），6．85（1H，ddd，J＝8Hz，2Hz，1Hz），7．09（1H，ddd，J＝8Hz，8Hz，1Hz），7．21－7．29（3H，m），7．52－7．59（2H，m），7．57（1H，d，J＝8Hz），7．63（1H，ddd，J＝8Hz，8Hz，1Hz），7．99（1H，dd，J＝8Hz，2Hz），8．41（1H，dd，J＝8Hz，1Hz），9．53（1H，s），10．03（1H，s）

IR（ν，cm^{-1}，KBr）：3380，3320，3244，3056，2212，1644，1594，1582，1558，1530，1500，1468，1442，1424，1334，1294，1226，1154，756

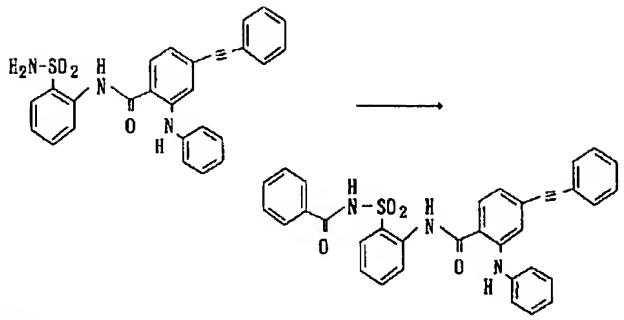
EI－MS（m／z，%）：467（m+，59），295（100），267（16）

融点：195－196℃

【0489】実施例74：N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）ベンゼンスルホニル］ベンズアミド

【0490】

【化120】



【0491】実施例73で製造した4－フェニルエチニル－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド200mg（0.43mmol）及び炭酸カリウム118mg（0.86mmol）をジオキサン（10ml）及び水10mlの混合溶液に、塩化ベンゾイル90mg（0.64mmol）を滴下し、室温で16時間撹拌した。反応溶液を1M－塩酸で酸性にした後、酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールで洗浄し、標記化合物168mg（収率69.0%）を得た。

【0492】NMR（$CDCl_3$）δ：7.00（1H，dd，J=8Hz，1Hz），7.07－7.12（1H，m），7.27－7.77（16H，m），7.92（1H，d，J=8Hz），8.07（1H，dd，J=8Hz，1Hz），8.62（1H，dd，J=8Hz，1Hz），8.70（1H，s），9.60（1H，s），10.49（1H，s）

IR（ν，cm^{-1}，KBr）：3384，3326，1704，1660，1596，1582，1562，1520，1286，752

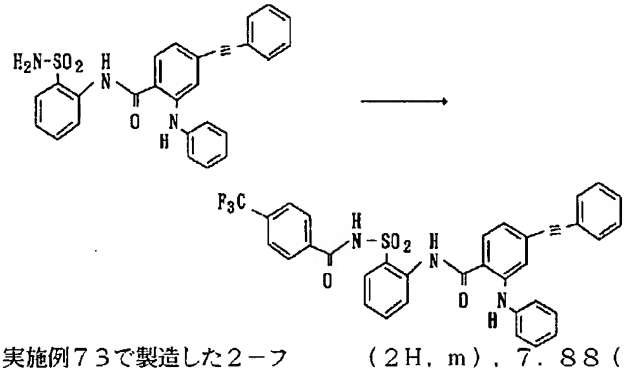
FAB－MS（m／z，%）：570（M－H，100）

融点241－243℃

【0493】実施例75：N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）ベンゼンスルホニル］－4－トリフルオロメチルベンズアミド

【0494】

【化121】



【0495】窒素気流下、実施例73で製造した2－フェニルアミノ－4－フェニルエチニル－N－（2－スルファモイルフェニル）ベンズアミド200mg（0.43mmol）及び、炭酸カリウム118mg（0.856mmol）のジオキサン（10ml）及び水（10ml）の混合溶液に、4－トリフルオロメチル塩化ベンゾイルを179mg（0.856mmol）を加え室温で16時間撹拌した。反応溶液を1M－塩酸で酸性にした後、酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をメタノールで洗浄し、目的物を168mg（収率61.0%）得た。

【0496】NMR（$CDCl_3$）δ：7.04－7.10（2H，m），7.21－7.25（2H，m），7.32－7.46（7H，m），7.55－7.60（2H，m），7.88（1H，d，J=8Hz），8.26（1H，dd，J=7Hz，2Hz），8.59（1H，dd，J=5Hz，2Hz），9.2－9.4（1H，m），11.4－11.6（1H，m）

IR（ν，cm^{-1}，KBr）：3320，3244，2216，1706，1662，1642，1594，1580，1558，1528，1498，1472，1442，1422，1326，1288，1256，1226，1156，1130，1070，756

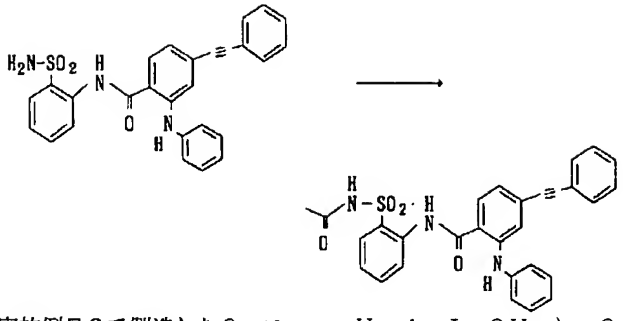
EI－MS（m／z，%）：639（m+，16），467（20），446（10），422（17），295（88），278（42）

融点：178－180℃

【0497】実施例76：N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）ベンゼンスルホニル］アセトアミド

【0498】

【化122】



【0499】窒素気流下、実施例73で製造した2－フェニルアミノ－4－フェニルエチニル－N－（2－スルファモイルフェニル）ベンズアミド400mg（0.86mmol）及び4－ジメチルアミノピリジン315mg（2.57mmol）のテトラヒドロフラン（10ml）溶液に無水酢酸0.12ml（1.28mmol）を加え、室温で2時間撹拌した。反応溶液を1M－塩酸で酸性にした後、酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィーで精製し、標記化合物358mg（収率82.2%）を得た。

【0500】NMR（$CDCl_3$）δ：2.08（3H, s），6.99（1H, dd, J=8Hz, 1Hz），7.07－7.12（1H, m），7.26－7.40（8H, m），7.46－7.54（3H, m），7.66－7.71（1H, m），7.82（1H, d, J=8Hz），8.01（1H, dd, J=8Hz, 1Hz），8.06－8.16（1H, m），8.58（1H, dd, J=8Hz, 1Hz），9.57（1H, s），10.30（1H, s）

IR（ν, cm^{-1}, KBr）：3450－2950, 2864, 2212, 1714, 1660, 1582, 1556, 1530, 1498, 1472, 1442, 1420, 1342, 1318, 1286, 1256, 1224, 1156, 1128, 854, 756

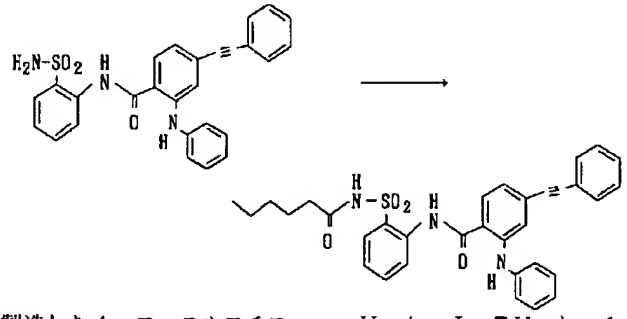
EI－MS（m／z, %）：509（m+, 22），295（49），267（7），91（2），61（3）

融点：108℃

【0501】実施例77：N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）ベンゼンスルホニル］ヘキサンアミド

【0502】

【化123】

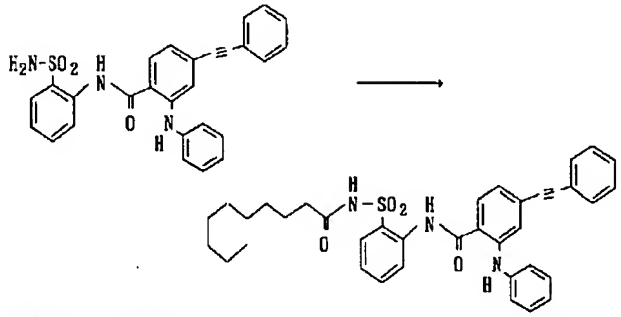


【0503】実施例73で製造した4－フェニルエチニル－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド500mg（1.04mmol）のテトラヒドロフラン（10ml）溶液に4－ジメチルアミノピリジン260mg（2.14mmol）、及びヘキサノイルクロリド0.16ml（1.17mmol）を加え、室温で1時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物200mg（収率33.3%）を得た。

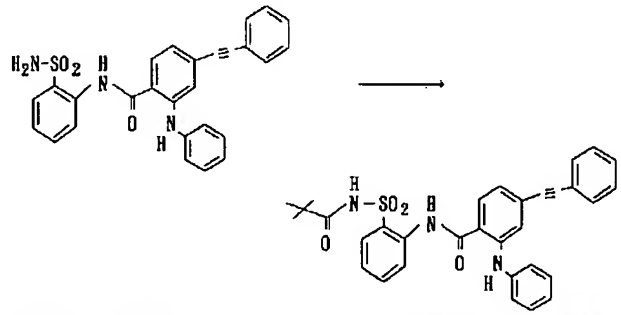
【0504】NMR（$CDCl_3$）δ：0.84（3H, t, J=7Hz），1.16－1.32（4H, m），1.50－1.62（2H, m），2.23（2H, t, J=7Hz），6.99（1H, dd, J=8Hz, 1Hz），7.06－7.12（1H, m），7.24－7.30（3H, m），7.32－7.40（5H, m），7.46－7.54（3H, m），7.65－7.71（1H, m），7.83（1H, d, J=8Hz），8.01（1H, dd, J=8Hz, 1Hz），8.10（1H, br－s），8.57（1H, dd, J=8Hz, 1Hz），9.57（1H, s），10.31（1H, s）

IR（ν, cm^{-1}, KBr）：2956, 1714, 1660, 1582, 1442, 1286, 756, 69

2
EI－MS（m／z，%）：565（m+，41），467（4），295（100），267（13），205（29）
【0505】実施例78：N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）ベンゼンスルホニル］デカンアミド
【0506】
【化124】



【0507】窒素気流下、実施例73で製造した2－フェニルアミノ－4－フェニルエチニル－N－（2－スルファモイルフェニル）ベンズアミド250mg（0．54mmol）及び炭酸カリウム148mg（1．07mmol）のジオキサン（10ml）及び水（10ml）の混合溶液に、デカノイルクロリド153mg（0．806mmol）を加え室温で20時間撹拌した。反応溶液に、1M－塩酸で酸性にした後、酢酸エチルで抽出した。有機層を水、飽和炭酸水素ナトリウム水溶液、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルカラムクロマトグラフィー（塩化メチレン）で精製し、標記化合物238mg（収率71．5%）を得た。
【0508】NMR（$CDCl_3$）δ：0．86（3H，t，J＝7Hz），1．12－1．32（11H，m），1．50－1．62（3H，m），2．23（2H，t，J＝7Hz），6．99（1H，dd，J＝8Hz，1Hz），7．09（1H，t，J＝7Hz），7．24－7．42（8H，m），7．47－7．68（1H，t，J＝7Hz），7．83（1H，d，J＝8Hz），8．00（1H，dd，J＝8Hz，1Hz），8．08（1H，s），8．57（1H，d，J＝8Hz），9．57（1H，s），10．32（1H，s）
IR（ν，cm^{-1}，KBr）：3252，2928，2856，2216，1714，1668，1594，1578，1564，1524，1500，1470，1440，1418，1342，1314，1286，1226，1156，870，754，724，690，582
EI－MS（m／z，%）：621（m+，50%），467（12），446（13），295（100），278（9），267（13）
【0509】実施例79：N－［2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）ベンゼンスルホニル］ピバルアミド
【0510】
【化125】



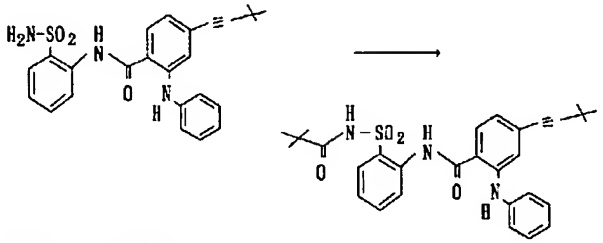
【0511】窒素気流下、実施例73で製造した2－フェニルアミノ－4－フェニルエチニル－N－（2－スルファモイルフェニル）ベンズアミド226mg（0．48mmol）及び、4－ジメチルアミノピリジン118mg（0．96mmol）のテトラヒドロフラン（10ml）溶液にピバロイルクロリド0．07ml（0．57mmol）を加え室温で1時間撹拌した後、溶媒を減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を1M－塩酸、水、及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製して、標記化合物150mg（収率56．0%）を得た。
【0512】NMR（$CDCl_3$）δ：1．14（9H，s），7．00（1H，dd，J＝8Hz，2Hz），7．09（1H，ddd，J＝8Hz，8Hz，2Hz），7．24－7．31（3H，m），7．33

－7．39（5H，m），7．48－7．53（3H，m），7．68（1H，dd，J＝8Hz，2Hz），7．83（1H，d，J＝8Hz），8．00（1H，dd，J＝8Hz，2Hz），8．18（1H，br－s），8．53（1H，dd，J＝8Hz，2Hz），9．57（1H，s），10．25（1H，s）
IR（ν，cm^{-1}，KBr）：2212，1704，1658，1582，1558，1532，1472，1442
EI－MS（m／z，%）：551（m+，49），521（30），295（100），195（48）
融点：223－224℃

【0513】実施例80：N－［2－［4－（3，3－ジメチルブチニル）－2－フェニルアミノベンズアミド］ベンゼンスルホニル］ピバルアミド

【0514】

【化126】



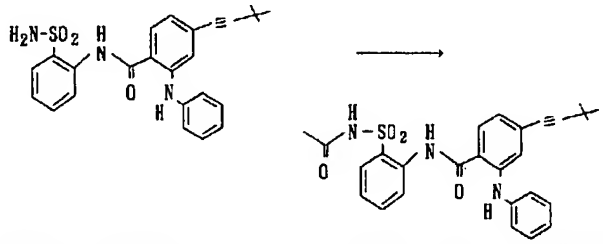
【0515】窒素気流下、実施例70で製造した4－（3，3－ジメチルブチニル）－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド200mg（0．45mmol）及び、4－ジメチルアミノピリジン110mg（0．9mmol）のテトラヒドロフラン（10ml）溶液にピバロイルクロリド0．06ml（0．49mmol）を加え室温で1時間撹拌した後、溶媒を減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製して、標記化合物180mg（収率75．0%）を得た。

【0516】NMR（$CDCl_3$）δ：1．12（9H，s），1．38（9H，s），6．87（1H，dd，J＝8Hz，2Hz），7．07（1H，ddd，J＝8Hz，8Hz，2Hz），7．22－7．29（3H，m），7．32－7．38（3H，m），7．67（1H，ddd，J＝8Hz，8Hz，2Hz），7．75（1H，d，J＝8Hz），7．99（1H，dd，J＝8Hz，2Hz），8．15（1H，br－s），8．50（1H，dd，J＝8Hz，2Hz）
9．519（1H，s），10，17（1H，s）
IR（ν，cm^{-1}，KBr）：2224，1714，1652，1594，1580，1564，1530，1498
EI－MS（m／z，%）：531（m+，85），175（100），260（53）
融点：218－219℃

【0517】実施例81：N－［2－［4－（3，3－ジメチルブチニル）－2－フェニルアミノベンズアミド］ベンゼンスルホニル］アセトアミド

【0518】

【化127】



【0519】窒素気流下、実施例70で製造した4－（3，3－ジメチルブチニル）－2－フェニルアミノ－N－（2－スルファモイルフェニル）ベンズアミド300mg（067mmol）及び、4－ジメチルアミノピリジン180mg（1．47mmol）のテトラヒドロフラン（10ml）溶液に無水酢酸0．07ml（0．74mmol）を加え室温で1時間撹拌した後、溶媒を減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次専用し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製して、標記化合物235mg（収率72．0%）を得た。

【0520】NMR（$CDCl_3$）δ：1．28（9H，s），2．04（3H，s），6．85（1H，dd，J＝8Hz，2Hz），7．07（1H，dd，J＝8Hz，8Hz），7．22－7．29（3H，m），7．31－7．39（3H，m），7．66（1H，ddd，J＝8Hz，8Hz，2Hz），7．73（1H，d，J＝8Hz），7．99（1H，dd，J

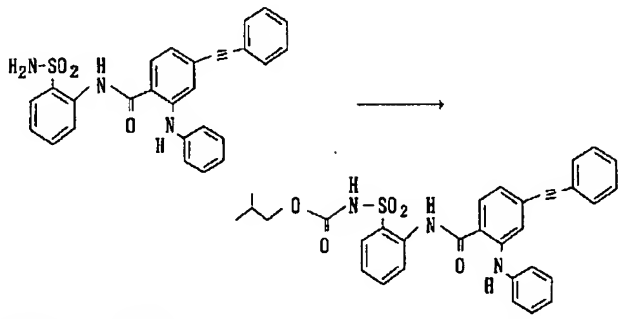
=8Hz，2Hz），8．26（1H，br－s），8．55（1H，dd，J=8Hz，2Hz）9．49（1H，s），10．24（1H，s）
IR（ν，cm^{-1}，KBr）：2224，1730，1658，1582，1556，1538，1498，1470，1442，1418，1336，1270
EI－MS（m／z，%）：489（m+，73），275（100），260（70）

融点：208－209℃

【0521】実施例82：N－［2－［（2－メチルプロピルオキシカルボニルアミノ）スルフォニル］フェニル］2－フェニルアミノ－4－フェニルエチニルベンズアミド

【0522】

【化128】



【0523】窒素気流下、実施例73で製造した2－フェニルアミノ－4－フェニルエチニル－N－（2－スルファモイルフェニル）ベンズアミド500mg（1．07mmol）及び、4－ジメチルアミノピリジン289mg（2．36mmol）のテトラヒドロフラン（10ml）溶液にクロロ炭酸イソブチル0．15ml（1．18mmol）を加え室温で1時間撹拌した後、溶媒を減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製して、標記化合物455mg（収率75．0%）を得た。

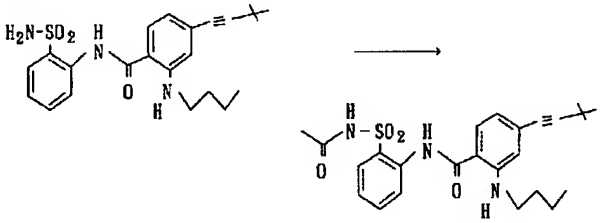
【0524】NMR（δ，$CDCl_3$）：0．83（6H，d，J=7Hz），1．80－1．90（1H，m），3．85（2H，d，J=7Hz），6．98（1H，dd，J=8Hz，2Hz），7．10（1H，ddd，J=8Hz，8Hz，2Hz），7．24－7．31（4H，m），7．32－7．39（4H，m），7．47－7．55（3H，m），7．60（1H，br－s），7．68（1H，ddd，J=8Hz，8Hz，2Hz），7．76（1H，d，J=8Hz），8．03（1H，dd，J=8Hz，2Hz），8．61（1H，dd，J=8Hz，2Hz），9．57（1H，s），10．27（1H，s）
IR（ν，cm^{-1}，KBr）：2212，1716，1674，1582，1556，1516，1472，1424，1356，1226
FAB－MS（m／z，%）：566（M－H，23），265（100）

融点：155－156℃

【0525】実施例83：N－［2－［2－ブチルアミノ－4－（3，3－ジメチルブチニル）ベンズアミド］ベンゼンスルホニル］アセトアミド

【0526】

【化129】



【0527】窒素気流下、2－ブチルアミノ－4－（3，3－ジメチルブチニル）－N－（2－スルファモイルフェニル）ベンズアミド300mg（0．70mmol）及び、4－ジメチルアミノピリジン189mg（1．55mmol）のテトラヒドロフラン（10ml）溶液に無水酢酸0．07ml（0．74mmol）を加え室温で1時間撹拌した後、溶媒を減圧下留去した。残留物に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製して、標記化合物250mg（収率76．0%）を得た。

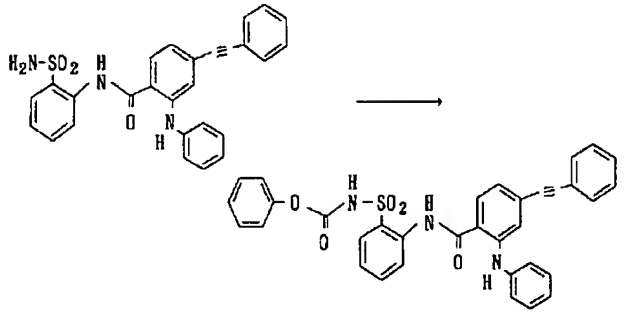
【0528】NMR（δ，$CDCl_3$）：0．96（3H，t，J=7Hz），1．33（9H，s），1．44－1．56（2H，m），1．63－1．70（2H，m），2．04（3H，s），3．18（2H，

t，J＝7Hz），6．66（1H，dd，J＝8Hz，2Hz），6．72（1H，d，J＝2Hz），7．24（1H，ddd，J＝8Hz，8Hz，2Hz），7．61（1H，d，J＝8Hz），7．65（1H，ddd，J＝8Hz，8Hz，2Hz），7．81（1H，br－s），8．01（1H，dd，J＝8Hz，2Hz），8．20（1H，br－s），8．48（1H，dd，J＝8Hz，1Hz），10．02（1H，s）
IR（ν，cm^{-1}，KBr）：3392，3196，2972，2932，2872，2228，1736，1640，1598，1584，1564，1530，1474，1444，1348，1290，1236，1212，1154，854，766
EI－MS（m／z，%）：489（m+，73），275（100），260（70）
融点：155－156℃

【0529】実施例84：2－フェニルアミノ－4－フェニルエチニル－N－［2－［（フェニルオキシカルボニルアミノ）スルフォニル］フェニル］ベンズアミド

【0530】

【化130】



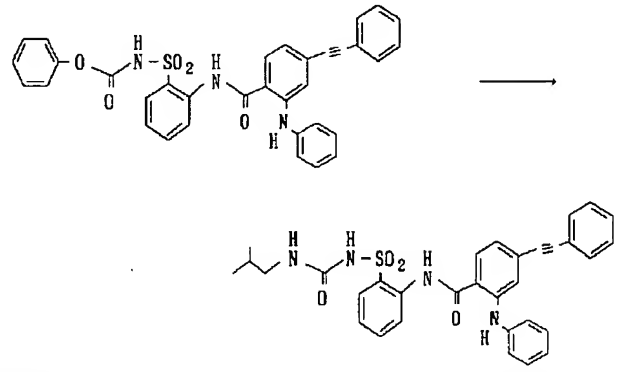
【0531】窒素気流下、実施例73で製造した2－フェニルアミノ－4－フェニルエチニル－N－（2－スルファモイルフェニル）ベンズアミド548mg（1．18mmol）及び、4－ジメチルアミノピリジン316mg（2．60mmol）の酢酸エチル（10ml）溶液にクロロ炭酸フェニル0．18ml（1．42mmol）を加え室温で1時間撹拌した。反応溶液を硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をエーテルで洗浄して、標記化合物520mg（収率75．0%）を得た。

【0532】NMR（$CDCl_3$）δ：6．96（1H，dd，J＝8Hz，2Hz），7，00－7．04（2H，m），7．11（1H，dd，J＝8Hz，8Hz），7．18－7．38，（11H，m），7．45（1H，d，J＝2Hz），7．49－7．53（2H，m），7．68－7．74（2H，m），7．82（1H，br－s），8．09（1H，dd，J＝8Hz，2Hz），8．63（1H，dd，J＝8Hz，1Hz），9．50（1H，s），10．23（1H，s）
IR（ν，cm^{-1}，KBr）：3392，3064，2864，2216，1748，1646，1582，1560，1528，1498，1476，1442，1420，1360，1320，1288，1226，1198，1162，1128，898，754
FAB－MS（m／z，%）：586（M－H，22），451（100）
融点：146－147℃

【0533】実施例85：2－フェニルアミノ－4－フェニルエチニル－N－［2－［［（2－メチルプロピルアミノ）カルボニルアミノ］スルホニル］フェニル］ベンズアミド

【0534】

【化131】



【0535】実施例84で製造した2－フェニルアミノ－4－フェニルエチニル－N－［2－［（フェニルオキ

シカルボニルアミノ）スルフォニル］フェニル］ベンズアミド105mg（0．18mmol）及び、イソブチルアミン0．04ml（0．36mmol）のベンゼン（5ml）溶液を2時間加熱還流した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルで再結晶して、標記化合物70mg（収率69．0%）を得た。

【0536】NMR（$CDCl_3$）δ：0．83（6H，d，J=7Hz），1．64－1．71（1H，m），2．91（2H，dd，J=7Hz，6Hz），6．23（1H，br－S），6．94（1H．dd，J=8Hz，2Hz），7．10（1H，ddd，J=8Hz，8Hz，1Hz），7．21－7．28（3H，m），7．32－7．40（5H，m），7．45（1H，d，J=2Hz），7．48－7．53（2H，m），7．66（1H，ddd，J=8Hz，8Hz，2Hz），7．69（1H，d，J=8Hz），7．88（1H，dd，J=8Hz．2Hz），8．36（1H，br－s），8．56（1H，dd，J=8Hz，1Hz），9．56（1H，s），10．00（1H，s）

IR（ν，cm^{-1}，KBr）：3392，3268，3064，2960，2932，2220，1682，1658，1580，1554，1530，1498，1472，1442，1418，1344，1320，1288，1224，1152，752

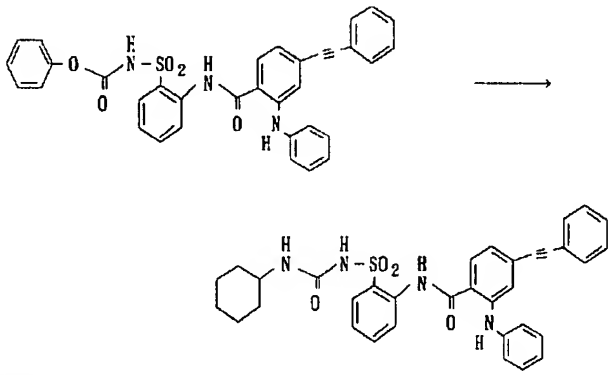
FAB－MS（m／z，%）：565（M－H，16），265（100）

融点：183－184℃

【0537】実施例86：N－［2－［［（シクロヘキシルアミノ）カルボニルアミノ］スルホニル］フェニル］2－フェニルアミノ－4－フェニルエチニルベンズアミド

【0538】

【化132】



【0539】実施例84で製造した2－フェニルアミノ－4－フェニルエチニル－N－［2－［（フェニルオキシカルボニルアミノ）スルフォニル］フェニル］ベンズアミド200mg（0．34mmol）及び、シクロヘキシルアミン0．09ml（0．75mmol）のベンゼン（5ml）溶液を2時間加熱還流した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルで再結晶して、標記化合物136mg（収率67．0%）を得た。

【0540】NMR（δ，$CDCl_3$）：1．06（2H，m），1．20－1．28（2H，m），1．45－1．70（4H，m），1．75－1．85（2H，m），3．45－3．55（1H，m），6．00（1H，br－S），6．96（1H，dd，J=8Hz，2Hz），7．11（1H，ddd，J=8Hz，8Hz，1Hz），7．24－7．30（5H，m），7．32－7．40（4H，m），7．46（1H，d，J=2Hz），7．49－7．53（2H，m），7．64－7．74（3H，m），7．89（1Hdd，J=8Hz，2Hz），8．57（1H，dd，J=8Hz，1Hz），9．55（1H，s），10．03（1H，s）

IR（ν，cm^{-1}，KBr）：3400，3316，3240，2940，2856，2212，1686，1662，1584，1556，1530，1498，1470，1444，1422，1338，1284，1252，1218，1154，1128，1028，756

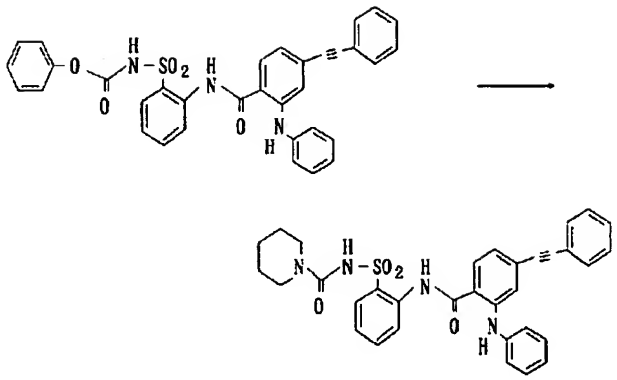
FAB－MS（m／z，%）：591（M－H，9），311（100）

融点：188－189℃

【0541】実施例87：2－フェニルアミノ－4－フェニルエチニル－N－［2－［（ピペリジノカルボニルアミノ）スルホニル］フェニル］ベンズアミド

【0542】

【化133】



【0543】実施例84で製造した2－フェニルアミノ－4－フェニルエチニル－N－[2－[（フェニルオキシカルボニルアミノ）スルフォニル]フェニル]ベンズアミド200mg（0.34mmol）及び、ピペリジン0.07ml（0.75mmol）のベンゼン（5ml）溶液を2時間加熱還流した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルで再結晶して、標記化合物94mg（収率50.0%）を得た。

【0544】NMR（δ，$CDCl_3$）：1.55（6H，br－S），3.32（4H，br－S），6.98（1H，dd，J＝8Hz，2Hz），7.08（1H，ddd，J＝8Hz，8Hz，1Hz），7.24－7.30（5H，m），7，31－7.39（4H，m），7.47－7.57（3H，m），7.64（1H，ddd，J＝8Hz，8Hz，2Hz），7.90（1H，d，J＝8Hz），8.00（1H，dd，J＝8Hz．2Hz），8.49（1H，dd，J＝8Hz，1Hz），9.64（1H，s），10.53（1H，s）

IR（ν，cm^{-1}，KBr）：3268，2940，2860，2212，1682，1660，1582，1562，1536，1498，1478，1442，1422，1316，1286，1256，1228，1160，752

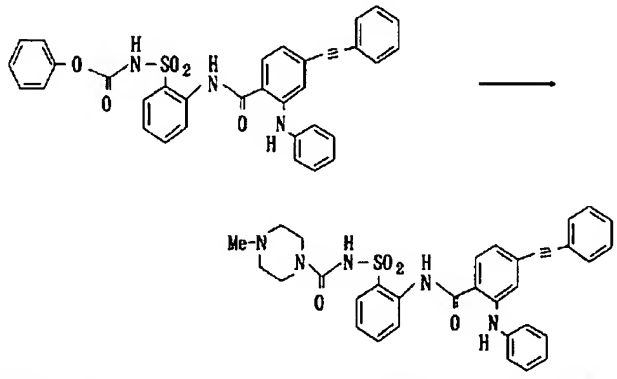
FAB－MS（m／z，%）：577（M－H，100），265（66）

融点：163－164℃

【0545】実施例88：N－[2－[[（4－メチルピペラジニル）カルボニルアミノ]スルホニル]フェニル]2－フェニルアミノ－4－フェニルエチニルベンズアミド

【0546】

【化134】

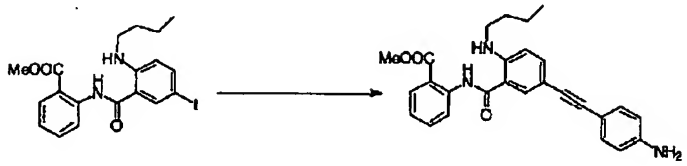


【0547】実施例84で製造した2－フェニルアミノ－4－フェニルエチニル－N－[2－[（フェニルオキシカルボニルアミノ）スルフォニル]フェニル]ベンズアミド160mg（0.27mmol）及び、1－メチルピペラジン0.07ml（0.75mmol）のベンゼン（5ml）溶液を2時間加熱還流した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水、硫酸水素カリウム水溶液及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をアセトニトリルで再結晶して、標記化合物130mg（収率81.0%）を得た。

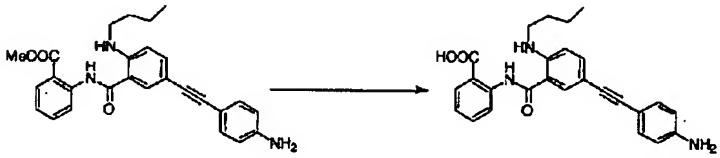
【0548】NMR（δ，$CDCl_3$）：2.23（4H，br－s），3.44（4H，br－s），6.84（1H，d，J＝8Hz），6.94－7.04（2H，m），7.16（2H，d，J＝8Hz），7.21－7.30（6H，m），7.34－7.44（4H，m），7.76（1H，d，J＝8Hz），7.93（1H，br－s），8.33（1H，d，J＝8Hz），9.56（1H，s），10.39（1H，s）

IR（ν，cm^{-1}，KBr）：3316，3056，2

940，2856，2800，2212，1660，1590，1556，1536，1498，1464，1442，1420，1320，1292，1266，1226，1142，1106，756
FAB－MS（m／z，%）：592（M－H，62），197（100）
融点：181－182℃
【0549】参考例44：2－［（4－アミノ）フェニルエチニル－2－ブチルアミノベンズアミド］安息香酸メチル
【0550】
【化135】



【0551】2－（2－ブチルアミノ－5－ヨードベンズアミド）安息香酸メチル300mg（0．66mmol）のジエチルアミン（12ml）及びテトラヒドロフラン（5ml）の混合溶液に4－エチニルアニリン200mg（1．72mmol）、ジクロロビストリフェニルホスフィンパラジウム23mg（0．03mmol）及びヨウ化銅12mg（0．06mmol）を加え、室温で20時間撹拌した後、溶媒を減圧下留去した。残留物に水を加えた後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物270mg（収率92．6%）を得た。
【0552】NMR（δ，$CDCl_3$）：0．97（3H，t，J＝7Hz），1．42－1．52（2H，m），1．64－1．72（2H，m），3．18－3．22（2H，m），3．78（2H，s），3．97（3H，s），6．63（2H，d，J＝8Hz），6．68（1H，d，J＝9Hz），7．08－7．14（1H，m），7．33（2H，d，J＝8Hz），7．46（1H，dd，J＝9，2Hz），7．55－7．61（1H，m），7．88（1H，d，J＝2Hz），7．95（1H，t，J＝5Hz），8．07（1H，dd，J＝8，1Hz），8．66－8．72（1H，d，J＝8Hz），11．71（1H，s）
【0553】実施例89：2－［（4－アミノ）フェニルエチニル－2－ブチルアミノベンズアミド］安息香酸
【0554】
【化136】



【0555】参考例44で製造した2－［（4－アミノ）フェニルエチニル－2－ブチルアミノベンズアミド］安息香酸メチル270mg（0．61mmol）のジオキサン（20ml）溶液に1M－水酸化ナトリウム水溶液3mlを加え、室温で24時間撹拌した。反応溶液に1M－塩酸を加え、酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物170mg（収率65．2%）を得た。
【0556】NMR（δ，$CDCl_3$）：0．98（3H，t，J＝7Hz），1．43－1．54（2H，m），1．64－1．74（2H，m），3．21（2H，t，J＝7Hz），6．57（2H，d，J＝8Hz），6．69（1H，d，J＝9Hz），6．97－7．04（1H，m），7．33（2H，d，J＝8Hz），7．47（1H，dd，J＝9，2Hz），7．57－7．64（1H，m），7．88（1H，d，J＝2Hz），8．01（1H，dd，J＝8，1Hz），8．78（1H，d，J＝8Hz），11．68（1H，s）
IR（ν，cm^{-1}，KBr）：3396，1652，1592，1528，1224，764
FAB－MS（m／z，%）：426（M－H，100）
融点：190　分解
【0557】参考例45：2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸エチル
【0558】
【化137】

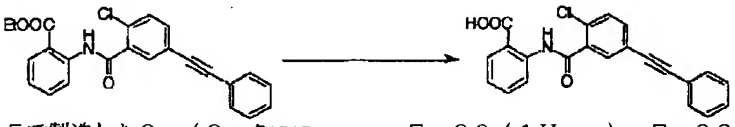
【0559】2－クロロ－5－フェニルエチニル安息香酸2．8g（10．91mmol）の無水ベンゼン（20ml）溶液に塩化チオニル2．0ml及びN，N－ジメチルホルムアミド数滴を加え、1時間加熱還流した後、溶媒を減圧下留去した。残留物を酢酸エチル（20ml）に溶解し、これを氷冷下炭酸カリウム2．3g（16．36mmol）、2－アミノ安息香酸エチル1．6ml（10．91mmol）の水（20ml）及び酢酸エチル（10）の混合溶液に滴下し、室温で18時間撹拌した。有機層を分離し、水層を酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し、標記化合物4．12g（収率93．5%）を得た。

【0560】NMR（δ，$CDCl_3$）：1．40（3H，t，J＝7Hz），4．37（2H，q，J＝7Hz），7．14－7．20（1H，m）7．34－7．40（3H，m），7．45（1H，d，J＝8Hz），7．50－7．58（3H，m），7．60－7．66（1H，m），7．80（1H，d，J＝2Hz），8．10（1H，dd，J＝8，1Hz），8．88（1H，d，J＝8Hz），11．57（1H，s）

【0561】参考例46：2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸

【0562】

【化138】



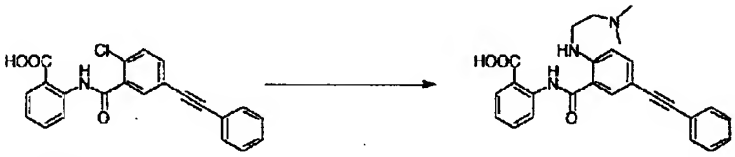
【0563】参考例45で製造した2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸エチル4．12g（10．20mmol）のエタノール（20ml）溶液に1M－水酸化ナトリウム水溶液30mlを加え、3時間加熱還流した。反応溶液に1M－濃塩酸を加え、酸性にした後、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物を酢酸エチル－ヘキサンにて再結晶し、標記化合物3．26g（収率85．0%）を得た。

【0564】NMR（δ，$CDCl_3$）：7．14－7．20（1H，m），7．33－7．38（1H，d，J＝8Hz），7．50－7．58（3H，m），7．64－7．70（1H，m），7．81（1H，d，J＝2Hz），8．12（1H，dd，J＝8，1Hz），8．98（1H，d，J＝8Hz），11．39（1H，s）

【0565】実施例90：2－［（2－ジメチルアミノ）エチルアミノ－5－フェニルエチニルベンズアミド］安息香酸

【0566】

【化139】



【0567】参考例46で製造した2－（2－クロロ－5－フェニルエチニルベンズアミド）安息香酸エチル0．90g（2．39mmol）のN，N－ジメチルエチレンジアミン（8ml）溶液に炭酸カリウム0．40g（2．87mmol）及び5wt．%の活性化銅を加え、封管中180℃で3時間加熱撹拌した後、室温まで冷却した。反応溶液に1M－塩酸を加え、酢酸エチルで抽出した。有機層を水及び飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後、溶媒を減圧下留去した。残留物をシリカゲルクロマトグラフィーで精製し標記化合物0．42g（収率41．1%）を得た。

【0568】NMR（δ，DMSO－d6）：2．83（6H，s），3．29（2H，t，J＝7Hz），3．64－3．74（2H，m），6．98（1H，d，J＝9Hz），7．19－7．26（1H，m），7．40－7．46（3H，m），7．49－7．55（2H，m），7．58（1H，dd，J＝9，2Hz），7．62－7．68（1H，m），7．91（1H，d，J＝2Hz），7．94－8．00（1H，m），8．04（1H，dd，J＝8，1Hz），8．53（1H，d，J＝8Hz），11．98（1H，s）

IR（ν，cm^{-1}，KBr）：2208，1680，1660，1592，1530，1228，754

FAB－MS（m／z，%）：426（M－H，100）
融点：181－183℃
【0569】薬理試験1：ACC阻害活性の測定
1．ACCの精製
12週齢の雄性SD系ラットを2日間絶食後、高ショ糖食（67%sucrose，17．1%casein，9．8%cellulose，5%salt，0．1%choline chloride，1%vitamins）を2日間与え、エーテル麻酔下に断頭、放血を行った後、速やかに肝臓を取り出した。氷冷した緩衝液A（225mM mannitol，75mM sucrose，10mM Tris／HCl（pH7．5），0．05mM EDTA－2Na，5mM potassium citrate，2．5mM $MnCl_2$，10mg／l aprotinin，10mg／l leupeptin，10mg／l antitrypsin）中でこの肝臓を細切し、水分を除去した後、5ml／gになるように緩衝液Aを加え、ポリトロンホモジナイザーで4分間ホモジナイズした。これを、1，000gで10分間遠心分離した後、上清を17，000gで10分間高速遠心分離した。
【0570】得られた上清を35%になるように硫酸アンモニウムを加え、45分間撹拌して、17，000gで10分間高速遠心分離した。得られた沈殿に100ml の緩衝液B（100mM Tris／HCl（pH7．5），0．5M NaCl，1mM EDTA－2Na，0．1mM DTT，10%glycerol，10mg／l aprotinin，10mg／l leupeptin，10mg／l antitrypsin）を加え、40，000gで20分間超遠心分離を行い、上清を150倍容の緩衝液C（100mM Tris／HCl（pH7．5），0．5M NaCl，1mM EDTA－2Na，0．1mM DTT，10%glycerol）で一晩透析し、5μM径のフィルターで沪過を行った。沪液をビオチンアフィニティーカラムにアプライし、緩衝液Bで洗浄した後に、5mMビオチンを含む緩衝液BでACCを溶出した。
【0571】2．ACC阻害活性の測定
前記実施例で製造した化合物をそれぞれDMSOに溶解しガラスバイアルに入れ、250μlのACCを含む試薬1（40mM Tris／HCl（pH7．5），40mM $MgCl_2$，40mM sodium citrate，2mM DTT，100μg／ml fatty acid free BSA）を加え、37℃で30分間恒温槽で加温し、氷冷後に74kBqの$NaH^{14}CO_3$を含む250μlの試薬2（40mM Tris／HCl（pH7．5），2mM DTT，8mM ATP，0．5mM acetyl CoA）を添加し、更に37℃で10分間恒温槽で加温した後に0．1mlの1N－HClを添加して反応を停止した。減圧下でガラスバイアル中の水分を完全に除去後、ガラスバイアルに乳化シンチレーター（クリアゾルI）を添加し、液体シンチレーションカウンターにて^{14}Cの放射能を測定した。各化合物の阻害活性（$5．6\times10^{-6}$mol）を求めた。その結果を表1に示す。
【0572】薬理試験2：細胞内脂肪酸合成に対する阻害活性（FA生合成阻害活性）合成の測定
前記実施例で製造した化合物をそれぞれDMSOで溶解し、実験培養液（DMEM，0．05μg／ml Insulin、0．1mg／ml glucose，18．5kBq／ml［^{14}C］－glucose）に添加した。$0．75\times10^6$ cells／mlに調製した。またHepG2細胞を、12well plateに1ml／wellで播種し、5%CO2，37℃で一晩培養後（培溶液：DMEM、4．5g／ml、グルコース、10%FBS）の細胞をPBS（－）緩衝液にて2度洗浄し、実験培養液を0．5ml／wellで添加した後、5%CO2，37℃で3時間培養した。培養後、氷冷したPBS（－）緩衝液で細胞を2度洗浄し、かきとった細胞の脂質を脂質抽出液（クロロホルム：メタノール＝2：1）にて抽出した。抽出物にエタノール2．5mlおよび33%水酸化カリウム0．1mlを加えて70℃で1時間湯浴した。この反応物から再び脂質を抽出し、抽出物をシリカゲル薄層板に適用した。これを展開液（ヘキサン：ジエチルエーテル：酢酸＝ 80：20：1）にて展開後、脂肪酸のヨウ素発色部位を採取し、その放射能を液体シンチレーションカウンターにて測定した。各化合物の阻害活性%（$3．0\times10^{-5}$M）を求めた。その結果を表1に示す。
【0573】
【表1】

実施例番号	化合物名	ACC阻害活性（%）（5.6×10^{-6}M）	FA合成阻害（%）（3.0×10^{-5}M）
7	2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）安息香酸	22．8	92．3
8	2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸	53．7	76．2
9	2－［4－フェニルエチニル－2－（3－トリフルオロメチルフェニルアミノ）ベンズアミド］安息香酸	61．3	66．5
15	2－（2－ヘキシルアミノ－4－フェニルエチニルベンズアミド）安息香酸	40．2	34．9
16	2－（2－ベンジルアミノ－4－フェニルエチニルベンズアミド）安息香酸	57．8	51．2
21	2－（2－n－オクチルアミノベンズアミド）安息香酸	41．5	37．2
22	2－（2－n－デシルアミノベンズアミド）安息香酸	37．3	36．0
30	2－（2，6－ジヘキシルアミノベンズアミド）安息香酸	38．4	91．6
31	2－［4－フェニルエチニル－2－（3－フェニルプロピルアミノ）ベンズアミド］安息香酸	93．7	50．5
33	2－（2－ブチルアミノ－4－フェニルエチニルベンズアミド）安息香酸	77．2	62．5
35	2－［5－フェニルエチニル－2－（3－フェニルプロピル）アミノベンズアミド］安息香酸	69．0	54．9
36	2－（2－フェニルアミノ－5－フェニルエチニルベンズアミド）安息香酸	87．8	82．8
37	2－（2－メチルアミノ－4－フェニルエチニルベンズアミド）安息香酸	41．7	78．6

【0574】　　【表2】

表1のつづき

実施例番号	化合物名	ACC阻害活性（%）（5.6×10^{-6}M）	FA合成阻害（%）（3.0×10^{-5}M）
40	2－[2－ブチルアミノ－5－（4－ニトロフェニル）エチニルベンズアミド]安息香酸	69.9	80.5
41	2－[2－ブチルアミノ－5－（4－シアノフェニル）エチニルベンズアミド]安息香酸	80.5	85.3
42	2－[2－ブチルアミノ－5－（4－ヒドロキシフェニル）エチニルベンズアミド]安息香酸	92.5	54.7
43	2－（2－メチルアミノ－5－フェニルエチニルベンズアミド）安息香酸	79.0	97.3
44	2－（2－エチルアミノ－5－フェニルエチニルベンズアミド）安息香酸	86.5	98.3
45	2－（2－プロピルアミノ－5－フェニルエチニルベンズアミド）安息香酸	87.6	95.0
46	2－（2－ブチルアミノ－5－フェニルエチニルベンズアミド）安息香酸	79.8	85.7
47	5－クロロ－2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）安息香酸	73.1	77.6
49	3－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）－2－ナフタレンカルボン酸	75.2	56.6
52	2－（4－ベンジルオキシ－2－フェニルアミノベンズアミド）－5－ヒドロキシ安息香酸	49.4	25.2
53	5－クロロ－2－（2－フェニルアミノ4－フェニルエチニルベンズアミド）安息香酸	84.1	64.4
55	3－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）－2－ナフタレンカルボン酸	58.9	42.4

【0575】　　【表3】

表1のつづき

実施例番号	化合物名	ACC阻害活性（%）（5.6×10^{-6}M）	FA合成阻害（%）（3.0×10^{-5}M）
56	5－メトキシ－2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸	76.3	53.6
57	5－メチル－2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸	78.0	67.6
59	3－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）チオフェンカルボン酸	55.1	85.3
60	5－ブロモ－2－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）安息香酸	82.2	67.1
61	1－（2－フェニルアミノ－4－フェニルエチニルベンズアミド）シクロヘキサンカルボン酸	30.0	70.3
62	2－［4－（オクタン－1－イル）－2－フェニルアミノフェニルアミノベンズアミド］安息香酸	67.4	70.2
63	2－［4－（3，3－ジメチルブチニル）－2－フェニルアミノベンズアミド］安息香酸	80.7	87.0
64	2－［2－フェニルアミノ－4－（ペンタン－1－イル）ベンズアミド］安息香酸	74.1	87.2
65	2－［2－ブチルアミノ－4－（3，3－ジメチルブチニル）ベンズアミド］安息香酸	48.5	59.6
66	2－［2－ブチルアミノ－5－（2－ピリジルエチニル）ベンズアミド］安息香酸	47.8	72.2
67	2－［2－ブチルアミノ－5－（2－チオフェニルエチニル）ベンズアミド］安息香酸	56.7	65.6
74	N－［2－（2－フェニルアミノ－4－フェニルニチニルベンズアミド）ベンゼンスルホニル］ベンズアミド	52.9	58.6

【0576】　　【表4】

表１のつづき

実施例番号	化合物名	ＡＣＣ阻害活性（％）（5.6×10^{-8}Ｍ）	ＦＡ合成阻害（％）（3.0×10^{-5}Ｍ）
７５	Ｎ－［２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）ベンゼンスルホニル］－４－トリフルオロメチルベンズアミド	２６．０	１４．６
７６	Ｎ－［２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）ベンゼンスルホニル］アセトアミド	８７．５	６９．４
７７	Ｎ－［２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）ベンゼンスルホニル］ヘキサンアミド	８８．１	８４．９
７８	Ｎ－［２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）ベンゼンスルホニル］デカンアミド	５９．５	１９．７
７９	Ｎ－［２－（２－フェニルアミノ－４－フェニルエチニルベンズアミド）ベンゼンスルホニル］ピバルアミド	８３．７	６４．９
８０	Ｎ－［２－［４－（３，３－ジメチルブチニル）－２－フェニルアミノベンズアミド］ベンゼンスルホニル］ピバルアミド	４９．７	６７．７
８１	Ｎ－［２－［４－（３，３－ジメチルブチニル）－２－フェニルアミノベンズアミド］ベンゼンスルホニル］アセトアミド	２８．０	８４．４
８２	Ｎ－［２－［（２－メチルプロピルオキシカルボニルアミノ）スルフォニル］フェニル］２－フェニルアミノ－４－フェニルエチニルベンズアミド	９１．９	６７．２

【０５７７】

【発明の効果】上記したように、本発明は心筋梗塞、脳梗塞、糖尿病等の成人病のリスクファクターとなる内臓脂肪症候群の治療に有効なＡＣＣ活性阻害剤としての上記一般式（Ｉ）で表される新規な芳香族アミド誘導体を提供するものであり、その医療上の効果は多大なものである。

フロントページの続き

(51)Int.Cl.[6]		識別記号	ＦＩ		
Ａ６１Ｋ	31/19		Ａ６１Ｋ	31/19	
	31/38			31/38	
	31/44			31/44	
	31/445	６０１		31/445	６０１
Ｃ０７Ｃ	255/58		Ｃ０７Ｃ	255/58	
	311/46			311/46	
	311/51			311/51	
Ｃ０７Ｄ	213/56		Ｃ０７Ｄ	213/56	
	213/80			213/80	
	295/14			295/14	Ｚ
	333/24			333/24	
	333/38			333/38	

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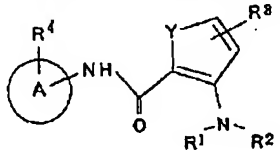
(57) (Abstract) (Amended)

Object

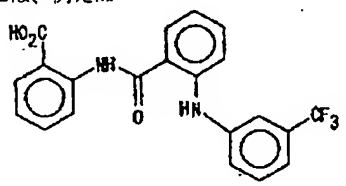
To put forward a novel aromatic amide derivative as ACC activity inhibiting agent effective in therapy of visceral fat syndrome which comprises a risk factor of adult diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like.

Method of Solution

An aromatic amide derivative represented by general formula,



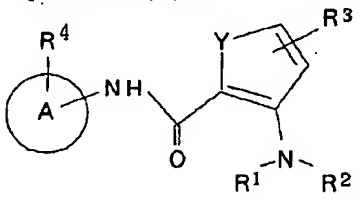
in an embodiment, represented by for example



Patent Claims

Claim 1

An aromatic amide derivative represented by general formula



(I)

(wherein, R1 and R2 denote hydrogen atom, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group. Furthermore, these R1 and R2 are not hydrogen atoms simultaneously, and moreover can form a 5-7 membered ring structure by bonding with nitrogen atom to which they are bonded and forming one body,

R3 denotes hydrogen atom, substituted amino group, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted alkenyl group of C2-C12, substituted or unsubstituted alkynyl group of C2-C12, substituted or unsubstituted alkoxy group of C1-C12, substituted or unsubstituted

aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group. Y denotes groups represented by -CH=CH-, -N=CH-, -CH=N-, sulphur atom or oxygen atom,
R4 denotes acid functional group
and ring A denotes substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted cyclic alkyl group).

Claim 2

An aromatic amide derivative in accordance with Claim 1, wherein the ring A is an aromatic hydrocarbon group having substitution at 1, 2 position, heteroaromatic ring group having substitution at 1, 2 position or cyclic alkyl group having substitution at 1, 1 position.

Claim 3

An aromatic amide derivative in accordance with Claim 2, wherein R3 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkenyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkynyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group or C1-C4 alkoxy group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, and R1 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent.

Claim 4

An aromatic amide derivative in accordance with Claim 2, wherein R3 is unsubstituted C5-C12 alkyl group, unsubstituted C5-C12 alkenyl group, unsubstituted C5-C12 alkynyl group or unsubstituted C5-C12 alkoxy group, and R1 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent.

Claim 5

An aromatic amide derivative in accordance with Claim 2, wherein R3 is hydrogen atom and R1 is substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted alkyl group of C4-C12.

Claim 6

An aromatic amide derivative in accordance with Claim 1, wherein acid functional group is carboxyl group.

Claim 7

An aromatic amide derivative in accordance with Claim 1, wherein acid functional group is a group represented by general formula R5CONHSO2- (wherein, R5 is substituted or unsubstituted alkyl group of C1-C12, aromatic hydrocarbon group, substituted amino group or substituted or unsubstituted alkoxy group of C1-C12).

Claim 8

A drug comprising an aromatic amide derivative in accordance with any of Claims 1-7 or a pharmacologically acceptable salt thereof as an effective ingredient.

Detailed Description of the Invention

(0001)

Technical Sphere of this Invention

This invention relates to an aromatic amide derivative, in detail, a novel aromatic amide derivative having Acetyl-CoA Carboxylase (hereinafter it may be abbreviated to ACC) inhibiting activity.

(0002)

Technology of the Prior Art

Recently, it became clear that excess accumulation of neutral fat, in particular, triglyceride in visceral adipose tissue is the main risk factor of various diseases such as hyperlipidemia, hypertension, arteriosclerosis, cardiac infarction, glucose tolerance aberration or the like. In other words, fatty acid synthesis is activated in visceral adipose tissue, and it is considered that if this fatty acid is discharged to portal vein, it accelerates insulin resistance and furthermore it is taken into liver, used as raw material of triglyceride and discharged in plasma, and hypertriglyceridemia is caused.

(0003)

On the other hand, ACC is an enzyme that catalyses synthesis of Malonyl-CoA from Acetyl-CoA and is the rate-limiting enzyme in biosynthesis of long chain fatty acid. Moreover, it is known that Malonyl-CoA itself synthesised from Acetyl-CoA by ACC regulates the Carnitine acyltransferase that participates in the consumption of free long chain fatty acid as energy source. Moreover, it is thought that activation of ACC participates in activation of fatty acid synthesis in visceral adipose tissue. Accordingly, a drug that hinders ACC activity hinders biosynthesis of long chain fatty acid in vivo and at the same time promotes metabolism, thereby the quantity of long chain fatty acid is decreased in vivo, as a result biosynthesis of triglyceride is inhibited, and it has possibility as prevention and treatment drug of various diseases based on accumulation of visceral fat.

(0004)

Problems to be Overcome by this Invention

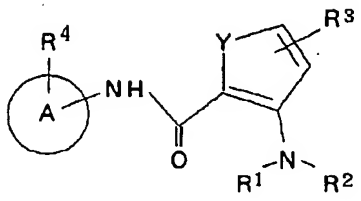
From such point of view, these inventors carried out assiduous investigations with an object to search ACC activity inhibiting agent effective in therapy of visceral fat syndrome comprising a risk factor of adult diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like, as a result, newly discovered that excellent ACC inhibiting action was observed in aromatic amide derivative represented by following general formula (I), and completed this invention. Accordingly, this invention has an object of putting forward a novel aromatic amide derivative and salts thereof, moreover putting forward a drug containing these compounds as active ingredient, in particular the ACC activity inhibiting agent.

(0005)

Means to Overcome these Problems

In order to solve such object, this invention puts forward an aromatic amide derivative represented by general formula,

(0006)



(I)

(0007)

(wherein, R1 and R2 denote hydrogen atom, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted

heteroaromatic ring group. Furthermore, this R1 and R2 are not hydrogen atom simultaneously, and moreover they can form 5-7 membered ring structure by bonding with nitrogen atom which they are bonded and forming one body, R3 denotes hydrogen atom, substituted amino group, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted alkenyl group of C2-C12, substituted or unsubstituted alkynyl group of C2-C12, substituted or unsubstituted alkoxy group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group. Y denotes groups represented by -CH=CH-, -N=CH-, -CH=N-, sulphur atom or oxygen atom, R4 denotes acid functional group and ring A denotes substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted cyclic alkyl group).

(0008)

Conditions for carrying out this invention

The aromatic amide derivative represented by aforesaid general formula (I) putting forward by this invention is a novel compound which has previously been unknown, and it has not been known that these compounds have ACC activity inhibiting action at all. However as it is made clear from results of later-described Pharmacological Test, it was revealed that these compounds had excellent ACC activity inhibiting action. Accordingly these compounds are extremely useful as ACC activity inhibiting agent effective in therapy in particular of visceral fat syndrome comprising a risk factor of geriatric diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like. Moreover as other embodiments thereof, this invention is to put forward a drug containing aromatic amide derivatives represented by the aforesaid general formula (I) or salts thereof as effective ingredient.

(0009)

Below the aromatic amide derivative putting forward by this invention will be described in greater detail. In this specification, as "alkyl group of C1-C12", it may be straight form, branched form or cyclic form, and methyl, ethyl, n-propyl, 1-methylethyl, cyclopropyl, n-butyl, 2-methylpropyl, 1-methylpropyl, 1,1-dimethylethyl, cyclobutyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, cyclopentyl, 2,2-dimethylpropyl, n-hexyl, 1-methyl pentyl, 2-methyl pentyl, 4-methyl pentyl. 1-ethyl butyl, 2-ethyl butyl, 3,3-dimethylbutyl, cyclohexyl, n-heptyl, 5-methyl hexyl, 4,4-dimethyl pentyl, cycloheptyl, 1-methyl hexyl, 2-methyl hexyl, 1-propyl butyl, 2-ethyl pentyl, cyclohexylmethyl, 1,1-diethyl propyl, n-octyl, 6-methylheptyl, cyclo octyl, 1-methylheptyl, 1-ethylhexyl, 5,5-dimethylhexyl, 2-cyclohexyl ethyl, n-nonyl, 1-methyl octyl, 7-methyl octyl, 6,6-dimethyl heptyl, n-decyl, 1-methyl nonyl, 8-methyl nonyl, 7,7-dimethyl octyl, n-undecyl, 1-methyl decyl, 9-methyl

decyl, 8,8-dimethyl nonyl, n-dodecyl, 1-methyl undecyl, 10-methyl undecyl, 5-methyl undecyl, 9,9-dimethyl decyl and the like can be exemplified, and furthermore, these alkyl group may be substituted by various kinds of substituents. As such substituent, halogen atom such as chlorine, bromine, iodine, fluorine or the like, aromatic hydrocarbon group such as nitro group, amino group, cyano group, hydroxy group, alkoxy group, thiol group, phenyl, naphthyl and the like, heteroaromatic ring group such as thienyl, furyl, pyridyl and the like can be exemplified. Moreover, these aromatic hydrocarbon groups and heteroaromatic ring group may further contain substituent such as the said halogen atom, alkyl group, alkoxy group, nitro group, amino group, cyano group, hydroxy group, thiol group and the like.

(0010)
Moreover, "substituted or unsubstituted aromatic hydrocarbon group" is monocyclic or polycyclic, and furthermore it denotes aromatic hydrocarbon group which may contain one or more various kinds of substituents on the ring, and for example phenyl, methylphenyl, dimethyl phenyl, methoxyphenyl, dimethoxyphenyl, nitrophenyl, dinitrophenyl, chlorophenyl, dichlorophenyl, bromo phenyl, dibromo phenyl, iodophenyl, fluorophenyl, trifluoromethylphenyl, aminophenyl, hydroxyphenyl, mercaptophenyl, cyanophenyl, alpha-naphthyl, beta-naphthyl group are nominated.

(0011)
The "substituted or unsubstituted heteroaromatic ring radical" is a group of 5 or 6 membered ring containing at least one of heteroatoms such as nitrogen atom, sulphur atom, oxygen atom or the like as ring constituting atoms, and these may be condensed with benzene ring and furthermore may contain one or more various kinds of substituents on ring, and for example pyridyl, furyl, thienyl, indolyl, quinolyl, isoquinolyl, benzofuranyl, benzothienyl, imidazolyl, benzimidazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrimidyl, pyrazyl, isoxazolyl, iso indolyl, pyrrolyl and the like are nominated.

(0012)
The "alkenyl group of C2-C12" may be branched chain or straight chain, and it is possibly exemplified by 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, ethenyl, 1-methyl ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 2-pentenyl, 1-pentenyl, 1,3-butane dienyl, 3-methyl butenyl, 1-hexenyl, 2-hexenyl, 3,3-dimethyl-1-butenyl, 4,4-dimethyl-1-pentenyl, 1,3-pentadienyl, 1,3-hexadienyl, heptenyl, octenyl, 2-cyclohexyl ethenyl nonenyl, decenyl, undecenyl, dodecenyl and the like, and furthermore, these alkenyl group may be substituted by various kinds of substituents. As the substituents, the same groups as substituents exemplified in aforesaid alkyl group of C1-C12 can be nominated.

(0013)

The "alkynyl group of C2-C12" may be branched chain or straight chain, and 1-propynyl, 2-propynyl, 1-methyl-2-propynyl, 1-ethyl-2-propynyl, ethynyl, 1-butynyl, 2-butynyl, 1,3-butadiynyl, 1-pentynyl, 2-pentynyl, 1,3-pentadiynyl, 1-hexynyl, 2-hexynyl, 1,3-hexadiynyl, 3,3-dimethyl-1-butynyl, heptynyl, octynyl, cyclohexyl ethynyl, nonynyl, decynyl, undecynyl, dodecynyl and the like are nominated, and furthermore, these groups may be substituted by various kinds of substituents. As the substituents, the same groups as substituents exemplified in aforesaid alkyl group of C1-C12 can be nominated.

(0014)

Moreover, "alkoxy group of C1-C12" denotes the alkyl-substituted oxy group in which alkyl group has aforesaid meaning, and embodiment examples include methoxy, ethoxy, n-propoxy, 1-methyl ethoxy, n-butoxy, 2-methyl propoxy, 1-methyl propoxy, 2-methyl-2-propoxy, 1,1-dimethyl ethoxy, n-pentyloxy, 3-methyl butoxy, 1-ethyl propoxy, n-hexyloxy, 3,3-dimethyl butoxy, heptyl oxy, 4-methyl pentoxy, cyclohexyl methoxy, octyloxy, nonyl oxy, decyloxy, undecyl oxy, dodecyl oxy and the like. Moreover, these alkyl group may be further substituted by various kinds of substituents. As the substituents, the same groups as substituents exemplified in aforesaid alkyl group of C1-C12 can be nominated.

(0015)

Moreover, "acid functional group" denotes hydroxy group, mercapto group, hydroxamic acid group, carboxyl group, phosphono group, sulfo group, sulphino group, sulpheno group, thio carboxyl group or amide, N-substituted amide and N-acylamido thereof. As N-acylamido group, for example groups represented by general formula R5CONHSO2- (wherein, R5 is substituted or unsubstituted alkyl group of C1-C12, aromatic hydrocarbon group, substituted amino group or substituted or unsubstituted alkoxy group of C1-C12) are nominated. As substituted amino group of R5, amino group wherein aforesaid substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted alkenyl group of C2-C12, substituted or unsubstituted alkynyl group of C2-C12, substituted or unsubstituted alkoxy group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group are substituted onto nitrogen atom with one or two substituents, and furthermore, the substituents may bond together with nitrogen atom to which they are bonded and form 5-7 membered saturated heterocycle structure including heteroatoms such as 1-pyrrolidinyl group, piperidino group, 1-piperazinyl group, morpholino group, thio morpholino group, 1-perhydroazepinyl group and the like can be nominated.

(0016)

As acid functional groups, examples include carboxamido, phosphonamide, sulfonamide, sulfine amide, sulphenamide, thiocarboxamide, N-benzoyl carboxamido, N-phenyl carboxamido, N-benzoyl sulfonamide, N-(3-benzyloxy benzoyl) sulfonamide, N-(4-trifluoromethyl benzoyl) sulfonamide, N-benzyl sulfonamide, N-phenyl sulfonamide, N-(4-nitrobenzoyl) sulfonamide, N-benzoyl phosphonamide, N-benzoyl sulfine amide, N-benzoyl thiocarboxy amide, N-acetyl sulfonamide, N-propanoyl sulfonamide, N-(2-methyl) propanoyl sulfonamide, N-butanoyl sulfonamide, N-hexanoyl sulfonamide, N-decanoyl sulfonamide, N-dodecanoyl sulfonamide, N-(2,2-dimethyl) propanoyl sulfonamide, N-(2-cyclohexyl) acetyl sulfonamide, N-phenyloxy carbonyl sulfonamide, N-benzyloxycarbonyl sulfonamide, N-methoxycarbonyl sulfonamide, N-ethoxycarbonyl sulfonamide, N-butoxycarbonyl sulfonamide, N-hexyloxy carbonyl sulfonamide, N-(2-methyl) propoxy carbonyl sulfonamide, N-(2,2-dimethyl) propoxy carbonyl sulfonamide, N-octyloxy carbonyl sulfonamide, N-decyloxy carbonyl sulfonamide, N-dodecyl oxycarbonyl sulfonamide, N-phenylamino carbonyl sulfonamide, N-benzylamino carbonyl sulfonamide, N-methylamino carbonyl sulfonamide, N-ethylamino carbonyl sulfonamide, N-butylamino carbonyl sulfonamide, N-(1-methyl) ethylamino carbonyl sulfonamide, N-(2-methyl) propylamino carbonyl sulfonamide, N-(2,2-dimethyl) propylamino carbonyl sulfonamide, N-hexyl aminocarbonyl sulfonamide, N-cyclohexyl aminocarbonyl sulfonamide, N-octyl aminocarbonyl sulfonamide, N-decyl aminocarbonyl sulfonamide, N-dodecyl aminocarbonyl sulfonamide, N-(1-piperidinyl carbonyl) sulfonamide, N-(1-piperazinyl carbonyl) sulfonamide, N-(4-morpholyl carbonyl) sulfonamide and the like.

(0017)

In aromatic amide derivative represented by the aforesaid general formula (I), substituents R1 and R2 may bond together with nitrogen atom to which they are bonded and form aforesaid 5-7 membered saturated heterocycle structure.

(0018)

In aromatic amide derivative represented by the aforesaid general formula (I) put forward by this invention, ring represented by A is aforesaid aromatic hydrocarbon group or heteroaromatic ring group. As the substituted manner of these groups, it is preferred that acid functional group represented by R4 and groups having amide side chain are substituted at 1,2 positions, and moreover when A is cyclic alkyl group, the acid functional group represented by R4 and groups having amide side chain are substituted at 1,1 position.

(0019)

Moreover, in aromatic amide derivative represented by the aforesaid general formula (I), when R3 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkenyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkynyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent or C1-C4 alkoxy group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, it is preferred that R1 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent.

(0020)

Moreover, when R3 is unsubstituted C5-C12 alkyl group, unsubstituted C5-C12 alkenyl group, unsubstituted C5-C12 alkynyl group or unsubstituted C5-C12 alkoxy group, it is preferred that R1 is C1-C4 alkyl group containing substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted aromatic hydrocarbon group as substituent. Furthermore when R3 is hydrogen atom, R1 is preferably substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted alkyl group of C4-C12. Moreover, it is preferred that acid functional group is group denoted by carboxyl group or general formula R5CONHSO2-.

(0021)

As aromatic amide derivative of this invention, for example following compounds are illustrated. 2-(2-(2-pyridyl) amino benzamide) benzoic acid, 2-(2-(2-thienyl) amino benzamide) benzoic acid, 2-(2-(2-furfuryl) amino benzamide) benzoic acid, 2-(2-butylamino benzamide) benzoic acid, 2-(2-octyl amino benzamide) benzoic acid, 2-(2-dodecyl amino benzamide) benzoic acid, 2-(2-cyclohexylamino benzamide) benzoic acid, 2-(2-(2-methylpropyl amino) benzamide) benzoic acid, 2-(2-(1-propyl butylamino) benzamide) benzoic acid, 2-(2-(3-methylbutyl amino) benzamide) benzoic acid, 2-(2-(1-methyl hexyl amino) benzamide) benzoic acid, 2-(2-(2-ethylhexyl amino) benzamide) benzoic acid, 2-(2-(2,2-dimethylpropyl amino) benzamide) benzoic acid, 2-(2-(3-phenylpropyl amino) benzamide) benzoic acid, 2-(2-(6-phenylhexyl amino benzamide) benzoic acid, 2-(2-[N-methyl-N-hexyl] amino benzamide) benzoic acid, 2-(2-iso indolyl benzamide) benzoic acid, 2-(2-butylamino benzamide)-4-nitrobenzoic acid, 2-(2-butylamino benzamide)-5-nitrobenzoic acid, 2-(2-butylamino benzamide)-5-trifluoromethyl benzoic acid, 2-(2-butylamino benzamide)-5-

hydroxybenzoic acid, 2-(2-butylamino benzamide)-5-methoxybenzoic acid, 2-(2-butylamino benzamide)-5-chlorobenzoic acid.

(0022)

2-(2-butylamino-4-phenethyl benzamide) benzoic acid, 2-(2-phenylamino-4-phenethyl benzamide) benzoic acid, 2-(2-butylamino-4-hexyl benzamide) benzoic acid, 2-(2-butylamino-4-decyl benzamide) benzoic acid, 2-(2-methylamino-4-phenylethenyl benzamide) benzoic acid, 2-(2-butylamino-4-phenylethenyl benzamide) benzoic acid, 2-(2-methylamino-4-benzyloxy benzamide) benzoic acid, 2-(2-butylamino-4-benzyloxy benzamide) benzoic acid, 2-(2-butylamino-4-cyclohexyl oxy benzamide) benzoic acid, 2-(2-butylamino-4-decyloxy benzamide) benzoic acid, 2-(2-(2-pyridyl) amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-thienyl) amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-furfuryl) amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-butylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-methylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-ethylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-propylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-octyl amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-decyl amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-benzylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-(3-phenylpropyl) amino-4-phenyl ethynyl benzamide) benzoic acid.

(0023)

2-(2-methylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-ethylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-propylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-octyl amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-benzylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-phenylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-phenylamino-3-phenyl ethynyl benzamide) benzoic acid, 2-(2-(3-phenylpropyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-hydroxyethyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-mercaptoethyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-amino ethyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-(N,N-dimethylamino) ethyl) amino-5-phenyl ethynyl benzamide) benzoic acid.

(0024)

2-(2,6-dihexyl amino benzamide) benzoic acid, 2-(2,6-diphenylamino benzamide) benzoic acid, 5-hydroxy-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-methyl-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-bromo-2-(2-phenylamino-4-phenyl ethynyl benzamide)

benzoic acid, 5-methoxy-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-amino-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-mercapto-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 3-(2-phenylamino-4-phenyl ethynyl benzamide) thiophene-2-carboxylic acid.

(0025)

5-methyl-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-bromo-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-methoxy-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-amino-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-mercapto-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 3-(2-phenylamino-4-benzyloxy benzamide) thiophene-2-carboxylic acid 2-(4-(1-octynyl)-2-phenylamino benzamide) benzoic acid, 2-(4-(1-pentynyl)-2-phenylamino benzamide) benzoic acid, 2-(4-(3,3-dimethylbutan-1-yl)-2-phenylamino benzamide) benzoic acid, 2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) benzoic acid, 2-(4-(3-cyclohexyl propan-1-yl)-2-phenylamino benzamide) benzoic acid, 2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) benzoic acid.

(0026)

2-(2-butylamino-4-(2-furfuryl) ethynyl benzamide) benzoic acid, 2-(2-phenylamino-5-(2-pyridyl) ethynyl benzamide) benzoic acid, 2-(2-phenylamino-5-(2-thienyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) benzoic acid, 2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) benzamide) benzoic acid, 2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(4-aminophenyl) ethynyl benzamide) benzoic acid.

(0027)

4-benzyloxy-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide, 2-butylamino-4-phenyl ethynyl-N-(2-sulphamoyl phenyl) benzamide, 2-(2-pyridyl) amino-4-phenyl ethynyl-N-(2-sulphamoyl phenyl) benzamide, 2-butylamino-4-(3,3-dimethylbutan-1-yl)-N-(2-sulphamoyl phenyl) benzamide, 4-(3,3-dimethylbutan-1-yl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide, N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) acetamide, N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) butane amide, N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) pivalamide, 2-methyl-N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) propanamide, N-(2-(2-butylamino-4-phenyl ethynyl benzamide)

phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) hexane amide.

(0028)
N-(2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) phenylsulfonyl) pivalamide, N-(2-(4-(3,3-dimethylbutan-1-yl)-2-phenylamino benzamide) phenylsulfonyl) acetamide, N-(2-(4-(1-octynyl)-2-phenylamino benzamide) phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-(1-octynyl) benzamide) phenylsulfonyl) acetamide, N-(2-(2-phenylamino-4-phenylethenyl benzamide) phenylsulfonyl) acetamide, N-(2-(4-(3,3-dimethylbutan-1-enyl)-2-phenylamino benzamide) phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-(1-octynyl) benzamide) phenylsulfonyl) acetamide, N-(2-((2-methyl) propyl oxycarbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((2,2-dimethyl) ethoxycarbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[phenyloxy carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[hexyloxy carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, 2-butylamino-N-((N-(2-methylpropyl) oxycarbonyl sulphamoyl) phenyl)-4-phenyl ethynyl benzamide, 2-butylamino-N-(2-[phenyloxy carbonyl sulphamoyl] phenyl)-4-phenyl ethynyl benzamide.

(0029)
N-(2-[methylamino carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((2-methyl) propylamino carbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[phenylamino carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[butylamino carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[cyclohexyl aminocarbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((1-piperidino) carbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((4-methylpiperazino) carbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide.

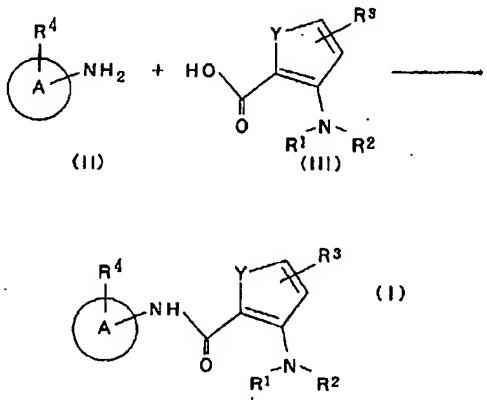
(0030)
When acid functional group of R4 is free carboxylic acid, sulfonic acid or the like, aromatic amide derivative of this invention may be used as drug of this invention in a form of acid itself or in a form of pharmacologically acceptable salt thereof. As such salts, conventionally used non-toxic salt, salt with inorganic base, for example alkali metal salt (for example sodium salt, potassium salt), alkaline earth metal salt (for example calcium salt, magnesium salt), ammonium salt, salt with organic base, for example organic amine salt (for example triethylamine salt, pyridine salt, picoline salt,

ethanolamine salt, triethanolamine salt, N,N-dimethylaminoethyl amine salt) or salt with basic amino acid and the like are nominated.

(0031)

Aromatic amide derivative of this invention can be produced according to for example following process. If a such process for the production is shown with chemical formula, it is summarised as follows.

(0032)



(0033)

In the formula, R1, R2, R3, R4, Y and ring A have the aforesaid meanings. In other words, aromatic amide derivative of this invention can be produced basically by condensing amino compound represented by formula (II) corresponding to the target compound of formula (I) and carboxylic acid compound represented by formula (III).

(0034)

This condensation reaction can be performed in the presence of condensing agent, and as condensing agent, it is possible to use for example carbodiimide reagent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and the like, carbonyldiimidazole, 2-chloro-1-methylpyridinium iodide salt.

(0035)

Moreover, it can be carried out by the method wherein carboxylic acid compound represented by formula (III) is converted into corresponding acid halide by the reaction with halogenation reagent such as thionyl chloride or phosphorus pentachloride and the like, or it is converted into an acid

anhydride which is a reactive body by using for example p-toluenesulfonic acid chloride, chlorocarbonic acid ethyl, pivaloyl chloride and the like, and thereafter caused to react with amino compound represented by formula (II).

(0036)
Moreover, as for this condensation reaction, it is possible to use a suitable solvent which is selected from inert solvent, for example ethers such as diethyl ether, tetrahydrofuran, dioxane and the like, aromatic hydrocarbon such as benzene, toluene, xylene and the like, hydrocarbon such as cyclopentane, cyclohexane and the like, halogenated hydrocarbon such as dichloro methane, dichloro ethane, trichloroethane, chloroform and the like, nitriles such as acetonitrile, propionitrile and the like, esters such as ethyl acetate and the like, N,N-dimethylformamide, dimethylsulfoxide and the like.

(0037)
Moreover, this condensation reaction can be performed in the presence of a base. As base, organic or inorganic base is nominated, for example alkali metal hydride such as sodium hydride, potassium hydride and the like, alkali metal hydroxide such as sodium hydroxide, potassium hydroxide and the like, alkali metal (or earth metal) carbonate such as sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate and the like, alkali metal hydrogencarbonate such as sodium bicarbonate, potassium bicarbonate and the like, alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium tertiary butoxide and the like, trialkylamine such as trimethylamine, triethylamine, N,N-diisopropyl-N-ethylamine and the like, pyridine compound such as pyridine, dimethylaminopyridine, picoline, lutidine and the like. The quantity of base, 1-10 times equivalent with respect to carboxylic acid compound is preferred.

(0038)
In this condensation reaction, the quantity of each of amino compound of formula (II) and carboxylic acid of formula (III) used is preferably almost equimolar amount. Moreover, the reaction temperature and the reaction time are not restricted, in particular depending on a kind of compound of formula (II) and (III) to be reacted, and the target compound can be obtained in a good yield by reacting for about 0.1-25 hours under the temperature condition of about 0 degrees to about boiling point of solvent used. Moreover, the quantity of use of condensing agent is prefebraly added 1-10 times equivalent with respect to compound of formula (II) and (III) to be reacted.

(0039)

On the other hand, in aromatic amide derivative represented by the aforesaid general formula (I) obtained by aforesaid condensation reaction, when substituent R4 is carboxylate ester, it can be derived to free carboxylic acid by ordinary ester hydrolysis reaction for example reaction with alkali such as sodium hydroxide solution, potassium hydroxide solution or the like in alcohol system solvent such as methanol, ethanol, propanol and the like. Moreover, in aromatic amide derivative represented by the aforesaid general formula (I), the compound in which substituent R4 is acyl sulfonamide group can be derived by reacting for example the compound in which substituent R4 of aromatic amide derivative represented by formula (I) obtained in above-mentioned condensation reaction is sulfonamide group with acyl halide in the presence of aforesaid suitable base in the aforesaid inert solvent.

(0040)

The target aromatic amide derivative represented by aforesaid general formula (I) can be obtained by suitably combining these aforesaid reactions, and in accordance with requirements, reaction solution can be isolated and purified by subjecting purification technique carried out usually, for example filtration, decantation, extraction, washing, solvent elimination by distillation, column or thin layer chromatography, recrystallisation, distillation and the like.

(0041)

When aromatic amide derivative or a pharmacologically acceptable salt thereof represented by the aforesaid general formula (I) of this invention is administered in a human as drug, although the dosage is different depending on the age or symptom of target disease, but preferably, it is orally-administered an effective dose, for example usually 5-30 mg per day divided into 1-3. It is possible that the drug of this invention is made formed into various kinds of pharmaceutical forms, oral administration formulation such as tablet, encapsulated formulation, granule, powder, troche agent, liquid agent and the like. These formulation can be carried out by itself familiar processed. For example, tablet, encapsulated formulation, granule, powder, troche agent and the like can be produced by formulating the compound of formula (I) of this invention by suitably combining with excipient such as starch, mannitol, lactose or the like, bonding agent such as carboxymethylcellulose sodium, hydroxypropylcellulose and the like, disintegrating agent such as crystalline cellulose, carboxymethylcellulose and the like, lubricant such as talc, magnesium stearate and the like, flowability improver such as light anhydrous silicic acid and the like, or the like.

(0042)

Moreover, drug of this invention can be formed into injection. This is pharmaceutically formulated, and for example, it is solubilised or dispersed in aqueous carrier such as physiological saline or the like, using detergent and dispersant and the beforehand, or moreover when required, injectable crystal formulation or lyophilization formulation is prepared, and solution or dispersion can be prepared at the time of use. A pH regulating agent and stabilising agent may be added as arbitrary component to aforesaid aqueous carrier. Dose and administration route of such injection are not restricted in particular, and the condition and characteristic of patient are taken into account, and a necessary dose can be administered safely by using intravenous drip infusion and also intraarterial, subcutaneous or intraperitoneal injection and the like.

(0043)

Examples

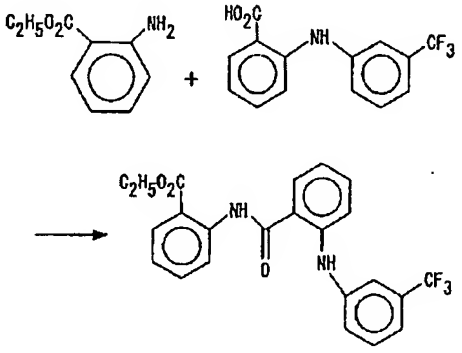
Below this invention is described in further detail by Reference Example, Example and Pharmacological Test Example. However, in the this invention, there are not any restrictions in any way by following description.

(0044)

Reference Example 1

2-(2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester.

(0045)



(0046)

Thionyl chloride 2.0 ml and several drops of N,N-dimethylformamide were added to anhydrous benzene solution (20 ml) of 2-(3-trifluoromethylphenyl amino) benzoic acid 1.5 g (5.33 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and next

excess thionyl chloride was eliminated by distillation under reduced pressure, and the residue was dissolved in benzene 10 ml, and under reduced pressure solvent was eliminated by distillation once again. The residue was dissolved in ethyl acetate 15 ml, and this was dropwise-added under ice cooling to mixed solution of 10 ml of ethyl acetate and 15 ml of water of potassium carbonate 1.30 g (10.67 mmol) and 2-ethyl aminobenzoic acid 0.78 ml (5.33 mmol) and was stirred at room temperature for four hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 1.82 g (yield 80.1 %) were obtained.

(0047)

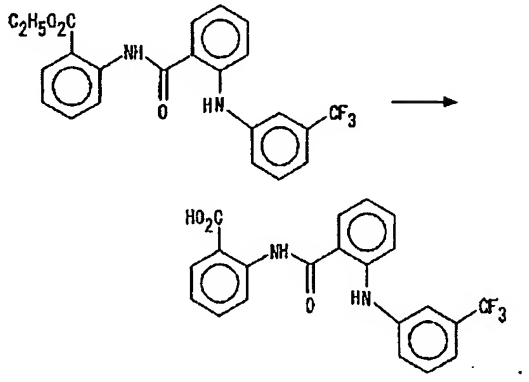
NMR (CDCl3) delta: 1.43 (3H, t, J = 7 Hz), 4.42 (2H, q, J = 7 Hz), 6.98 (1H, ddd, J = 8 Hz, 6 Hz, 2 Hz), 7.14 (1H, t, J = 8 Hz), 7.19-7.26 (1H, m), 7.34-7.44 (4H, m), 7.47 (1H, s), 7.60 (1H, dt, J = 8 Hz, 1 Hz), 7.84 (1H, d, J = 8 Hz), 8.11 (1H, dd, J = 8 Hz, 1 Hz), 8.79 (1H, d, J = 8 Hz), 9.76 (1H, s), 12.00 (1H, s).

(0048)

Example 1

2-(2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid.

(0049)



(0050)

1N-sodium hydroxide solution 15 ml were added to ethanol solution (15 ml) of 2-(2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester 0.66 g produced in Reference

Example 1 (1.54 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and ethanol was eliminated by distillation under reduced pressure, and the residue was extracted with ether. The organic layer was washed successively with 1N-hydrochloric acid and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was recrystallised from ether-hexane, and title compound 0.44 g (yield 71.6 %) were obtained.

(0051)

NMR (CDCl3) delta: 6.96 (1H, ddd, J = 8 Hz, 6 Hz, 2 Hz), 7.15-7.29 (2H, m), 7.35-7.45 (4H, m), 7.48 (1H, s), 7.68 (1H, dt, J = 8 Hz, 1 Hz), 7.79 (1H, d, J = 8 Hz), 8.19 (1H, d, J = 8 Hz), 8.83 (1H, d, J = 8 Hz), 9.70 (1H, s), 11.73 (1H, s).

IR (ν, cm-1, KBr): 3500-2600, 1708, 1652, 1612, 1582, 1456, 1336, 1210, 1112,752,740 MS (m/z, %): 400 (M+, 50), 382 (6), 263 (100), 264 (48).

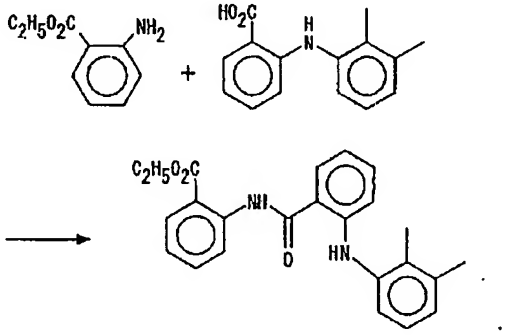
mp: 189-192 degrees.

(0052)

Reference Example 2

2-(2-(2,3-dimethyl phenylamino) benzamide) benzoic acid ethyl ester.

(0053)



(0054)

Thionyl chloride 2.0 ml and several drops of N,N-dimethylformamide were added to anhydrous benzene solution (20 ml) of 2-(2,3-dimethyl phenylamino) benzoic acid 2.0 g (8.29 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and next excess thionyl chloride was eliminated by distillation under reduced pressure, and the residue was dissolved in benzene 10 ml, and under reduced pressure solvent was eliminated by distillation once again. The

residue was dissolved in ethyl acetate 10 ml, and this was dropwise-added under ice cooling to mixed solution of ethyl acetate (10 ml) and 15 ml of water containing potassium carbonate 2.1 g (17.41 mmol) and 2-ethyl aminobenzoic acid 1.2 ml (8.29 mmol) and was stirred at room temperature for three hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 1.3 g (yield 40.4 %) were obtained.

(0055)

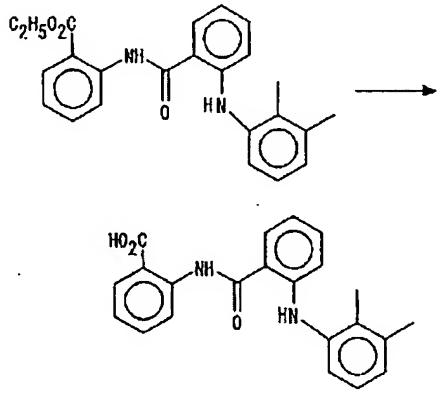
NMR (CDCl3) delta: 1.44 (3H, t, J = 7 Hz), 2.22 (3H, s), 2.33 (3H, s), 4.43 (2H, q, J = 7 Hz), 6.81 (1H, dt, J = 7 Hz, 1 Hz), 6.88 (1H, d, J = 8 Hz), 6.98 (1H, d, J = 7 Hz), 7.04-7.30 (4H, m), 7.59 (1H, dt, J = 8 Hz, 1 Hz), 7.82 (1H, dd, J = 8 Hz, 1 Hz), 8.11 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, d, J = 8 Hz), 9.48 (1H, s), 11.96 (1H, s).

(0056)

Example 2

2-(2-(2,3-dimethyl phenylamino) benzamide) benzoic acid.

(0057)



(0058)

1N-sodium hydroxide 15 ml were added to methanol solution (15 ml) of 2-(2-(2,3-dimethyl phenylamino) benzamide) benzoic acid ethyl ester 0.61 g (1.84 mmol) produced in Reference Example 2, and the mixture was heated under reflux for three hours. It was cooled to room

temperature, and methanol was eliminated by distillation under reduced pressure, and the residue was extracted with ether. The organic layer was washed successively with 1N-hydrochloric acid and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was recrystallised from ether-hexane, and title compound 0.34 g (yield 60.2 %) were obtained.

(0059)

NMR (CDCl3) delta: 2.22 (3H, s), 2.33 (3H, s), 6.79 (1H, t, J = 8 Hz), 6.89 (1H, d, J = 8 Hz), 6.99 (1H, d, J = 7 Hz), 7.09 (1H, t, J = 8 Hz), 7.13-7.22 (2H, m), 7.23-7.31 (1H, m), 7.67 (1H, dt, J = 8 Hz, 1 Hz), 7.76 (1H, d, J = 7 Hz), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.87 (1H, d, J = 8 Hz), 9.43 (1H, s), 11.69 (1H, s).

IR (ν, cm-1, KBr): 3380, 3500-2400, 1696, 1646, 1582, 1294, 1254, 1212,754,650 MS (m/z, %): 360 (M+, 58), 342 (8), 223 (100), 224 (43).

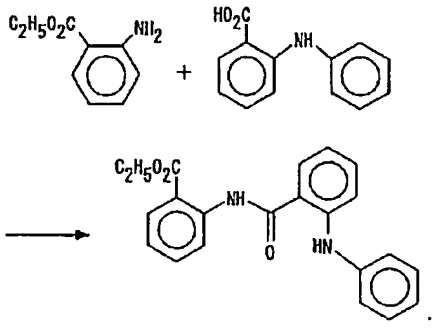
mp: 107-108 degrees.

(0060)

Reference Example 3

2-(2-phenylamino benzamide) benzoic acid ethyl ester.

(0061)



(0062)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide were added to anhydrous benzene solution (10 ml) of 2-phenylamino benzoic acid 0.50 g (2.34 mmol) and were heated under reflux for two hours, and the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in benzene 10 ml, and solvent was eliminated under reduced pressure by distillation once again. The residue was dissolved in ethyl acetate 10 ml, and this was dropwise-

added under ice cooling to mixed solution of ethyl acetate 10 ml and 15 ml of water containing potassium carbonate 0.65 g (4.69 mmol) and 2-ethyl aminobenzoic acid 0.34 ml (2.25 mmol) and was stirred at room temperature for 18 hours. Thereafter, the organic layer was washed successively with water, 1N-hydrochloric acid, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 0.36 g (yield 42.2 %) were obtained.

(0063)

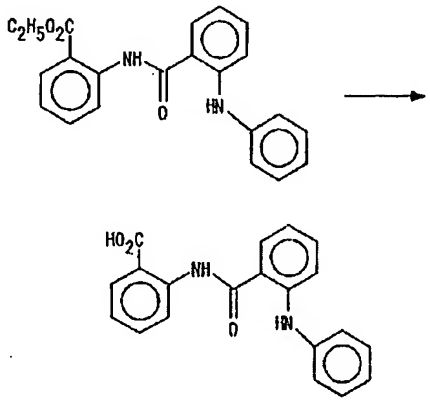
NMR (CDCl3) delta: 1.43 (3H, t, J = 7 Hz), 4.42 (2H, q, J = 7 Hz), 6.88 (1H, dt, J = 7 Hz, 1 Hz), 7.03 (1H, t, J = 7 Hz), 7.12 (1H, t, J = 7 Hz), 7.20-7.43 (6H, m), 7.59 (1H, dt, J = 8 Hz, 1 Hz), 7.81 (1H, d, J = 8 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, d, J = 8 Hz), 9.63 (1H, s), 11.94 (1H, s).

(0064)

Example 3

2-(2-phenylamino benzamide) benzoic acid.

(0065)



(0066)

1N sodium hydroxide 15 ml were added to methanol solution of 2-(2-phenylamino benzamide) benzoic acid ethyl ester 0.14 g (0.337 mmol) produced in Reference Example 3 and were heated under reflux for two hours. Methanol was eliminated by distillation under reduced pressure and was washed with ether. Concentrated hydrochloric acid was dropwise-added under ice cooling to the aqueous layer, and it was acidified, and next it was extracted twice with acetic acid ethyl ester. The

organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.10 g (yield 74.2 %) were obtained.

(0067)

NMR (DMSO-d6) delta: 6.91-7.04 (2H, m), 7.15-7.26 (3H, m), 7.26-7.37 (3H, m), 7.42 (1H, dt, J = 8 Hz, 1 Hz), 7.65 (1H, dt, J = 8 Hz, 1 Hz), 7.78 (1H, d, J = 7 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 9.30 (1H, s), 12.01 (1H, s).

IR (v, cm-1, KBr): 3372, 3400-2700, 1696, 1646, 1584, 1504, 1452, 1210,750 MS (m/z, %): 332 (M+, 58), 314 (5), 195 (100), 223 (14), 196 (50), 167 (30).

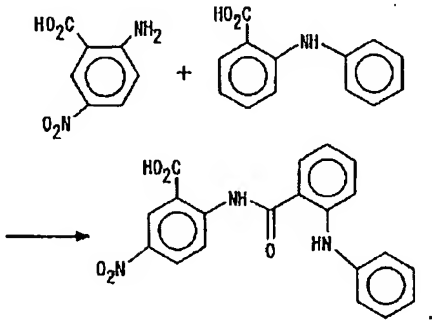
mp: 239-240 degrees.

(0068)

Example 4

5-nitro-2-(2-phenylamino benzamide) benzoic acid.

(0069)



(0070)

Thionyl chloride 0.26 ml (3.51 mmol) were added to anhydrous benzene solution (10 ml) of 2-phenylamino benzoic acid 0.50 g (2.34 mmol) and were stirred with room temperature for two hours, and under reduced pressure solvent was eliminated by distillation. Methylene chloride solution of the residue (10 ml) was dropwise-added under ice cooling to 2-amino-5-nitrobenzoic acid 427 mg (2.34 mmol) and methylene chloride (100 ml) solution of triethylamine 0.65 ml (4.68 mmol) and was stirred at room temperature for 18 hours. The organic layer was washed successively with water, 1N-hydrochloric acid and saturated aqueous sodium chloride solution, and it was dried with anhydrous

sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 300 mg (yield 34 %) were obtained.

(0071)

NMR (CDCl3) delta: 6.95-7.01 (2H, m), 7.17 (2H, d, J = 7 Hz), 7.28-7.34 (3H, m), 7.45 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.79 (1H, d, J = 7 Hz), 8.49 (1H, dd, J = 7 Hz, 2 Hz), 7.76 (1H, d, J = 7 Hz), 8.76 (1H, d, J = 2 Hz), 8.86 (1H, dd, J = 7 Hz, 2 Hz), 9.20 (1H, br-s), 12.41 (1H, br-s).

IR (ν, cm-1, KBr): 1706, 1646, 1598, 1574, 1556, 1498, 1450, 1346, 1286,1254.

EI-MS (m/z, %): 377 (M+, 48), 347(II), 197 (10), 196 (78), 168 (8).

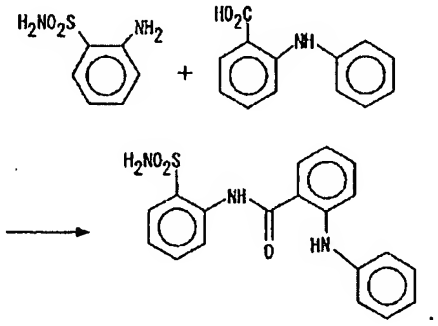
mp: 232-233 degrees.

(0072)

Example 5

2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0073)



(0074)

Thionyl chloride 0.26 ml (6.9 mmol) were added to anhydrous benzene solution (10 ml) of 2-phenylamino benzoic acid 1 g (4.6 mmol) and were stirred with room temperature for two hours, and under reduced pressure solvent was eliminated by distillation. Methylene chloride solution of the residue (10 ml) was dropwise-added under ice cooling in pyridine (10 ml) solution of 2-aminobenzene sulfonamide 808 mg (4.6 mmol) and was stirred at room temperature for 18 hours, and methylene chloride was eliminated by distillation. The residue was extracted with ethyl acetate, and it was washed successively with water, 1N-hydrochloric acid and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 1.2 g (yield 70 %) were obtained.

(0075)

NMR (CDCl3) delta: 4.89 (2H, br-s), 6.86 (1H, ddd, J = 6 Hz, 6 Hz, 1 Hz), 7.06 (1H, ddd, J = 6 Hz, 6 Hz, 1 Hz), 7.21-7.30 (7H, m), 7.63 (1H, dd, J = 6 Hz, 6 Hz), 7.67 (1H, d, J = 6 Hz), 7.97 (1H, d, J = 6 Hz), 8.40 (1H, d, J = 6 Hz), 9.49 (1H, br-s), 9.87 (1H, br-s).

IR (ν, cm-1, KBr): 1644, 1580, 1516, 1506, 1472, 1414, 1332, 1290, 1258, 1222, 1168,1156.

EI-MS (m/z, %): 367 (M+, 52), 236 (17), 196 (65), 195 (100), 167 (37).

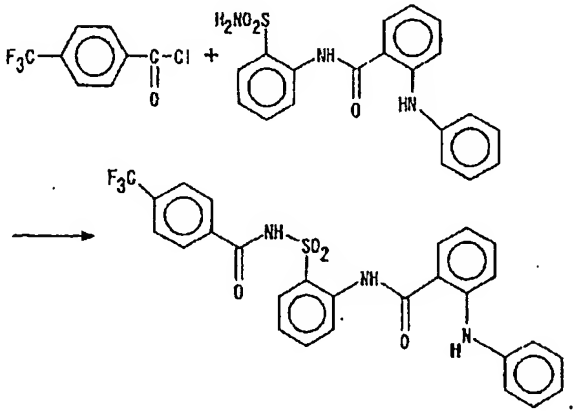
mp: 126-127 degrees.

(0076)

Example 6

N-(2-(4-benzyloxy-2-phenyl amino benzoamide) benzene sulphonyl) benzamide.

(0077)



(0078)

4-benzyloxy-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 300 mg (0.82 mmol) produced in Example 5, 4-trifluoromethyl benzoyl chloride 0.24 ml (1.64 mmol) and water-dioxane 1=1 solution (10 ml) of potassium carbonate 340 mg (2.4 mmol) were stirred for 18 hours. The solvent was eliminated by distillation, and the residue was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 200 mg (yield 45 %) were obtained.

(0079)

NMR (CDCl3) delta: 6.92 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.00 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.17 (2H, d, J = 7 Hz), 7.29-7.45 (5H, m), 7.64-7.70 (3H, m), 7.95 (1H, dd, J = 7 Hz, 1 Hz), 7.96-8.10 (3H, m), 8.23 (1H, d, J = 7 Hz), 9.40 (1H, br-s), 10.65 (1H, br-s).

IR (ν, cm-1, KBr): 1696, 1662, 1644, 1580, 1518, 1474, 1452, 1324, 1288.

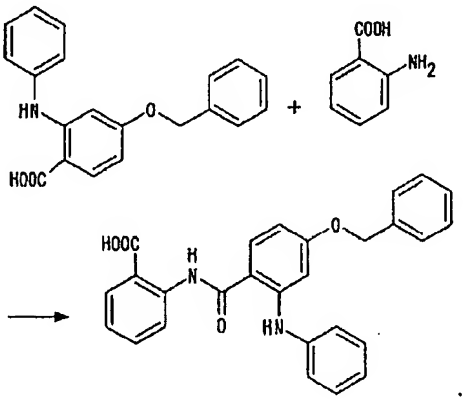
EI-MS (m/z, %): 539 (M+, 25), 288 (6), 197 (7), 196 (57), 195 (100), 173 (9), 169 (8).

(0080)

Example 7

2-(4-benzyloxy-2-phenylamino benzamide) benzoic acid.

(0081)



(0082)

Thionyl chloride 0.04 ml (0.50 mmol) were added under a nitrogen atmosphere in methylene chloride (10 ml) solution of 2-phenylamino-4-benzyloxy benzoic acid 100 mg (0.31 mmol), and it was stirred for one hour at room temperature, and next the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and this was dropwise-added under ice cooling to triethylamine 0.2 ml (1.30 mmol), methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.04 g (0.31 mmol) and was stirred at room temperature for 18 hours. 1N-hydrochloric acid was added, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by

distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 38 mg (yield 27.7 %) were obtained.

(0083)

NMR (CDCl3) delta: 5.04 (2H, s), 6.49 (1H, dd, J = 9 Hz, 2 Hz), 6.86 (1H, d, J = 2 Hz), 7.05 (1H, t, J = 7 Hz), 7.11-7.18 (3H, m), 7.25-7.42 (7H, m), 7.64 (1H, dt, J = 8 Hz, 1 Hz), 7.73 (1H, d, J = 9.0 Hz), 8.15 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, d, J = 8 Hz), 9.93 (1H, s), 11.64 (1H, s).

IR (ν, cm-1, KBr): 3500-2500, 1682, 1652, 1580, 1524, 1452, 1254, 752.

EI-MS (m/z, %): 438 (M+, 20), 420 (43), 302(11), 301 (16), 211 (9), 91 (100).

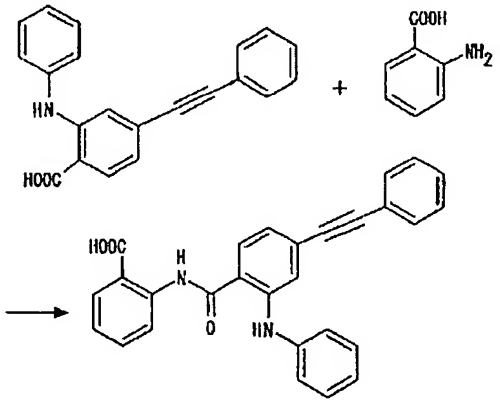
mp: 203-204 degrees.

(0084)

Example 8

2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0085)



(0086)

Thionyl chloride 0.15 ml (1.90 mmol) were added under a nitrogen atmosphere to methylene chloride (10 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 200 mg (0.64 mmol), and it was stirred for one hour at room temperature, and next the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and this was dropwise-added under ice cooling to triethylamine 0.36 ml (2.55 mmol), methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.09 g (0.64 mmol) and was stirred at room temperature for 18 hours. 1N-hydrochloric acid was added, and extraction was carried out with acetic acid ethyl ester.

The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and thereafter, it was recrystallised with acetonitrile, and title compound 37 mg (yield 13.4 %) were obtained.

(0087)

NMR (DMSO-d6) delta: 7.06 (1H, t, J = 7 Hz), 7.11 (1H, dd, J = 8 Hz, 1 Hz), 7.19-7.27 (3H, m), 7.32-7.46 (6H, m), 7.54-7.60 (2H, m), 7.65 (1H, dt, J = 8 Hz, 1 Hz), 7.82 (1H, d, J = 8 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.57 (1H, d, J = 8 Hz), 9.36 (1H, s), 12.08 (1H, s)

IR (ν, cm-1, KBr): 3324, 3400-2300, 1682, 1650, 1582, 1556, 1416, 1266,756.

EI-MS (m/z, %): 432 (M+, 23), 414 (100), 295 (55), 188 (65), 187 (58).

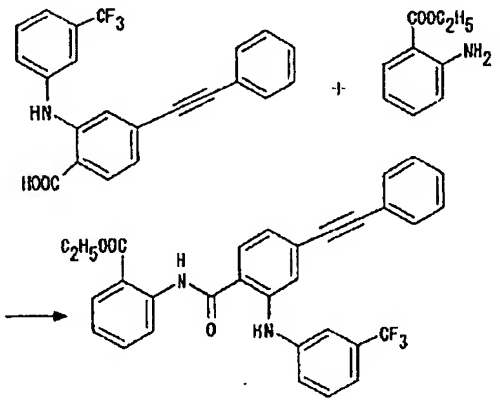
mp: 220-223 degrees.

(0088)

Reference Example 4

2 (4-phenyl-ethynyl-2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester.

(0089)



(0090)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide were added to anhydrous benzene solution (10 ml) of 4-phenyl-ethynyl-2-(3-trifluoro phenylamino) benzoic acid 250 mg (0.66 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and next excess thionyl chloride was eliminated by distillation under reduced pressure. The residue

was dissolved in benzene 10 ml, and solvent was eliminated under reduced pressure by distillation once again. The residue is dissolved in ethyl acetate 10 ml. Mixed solution of 10 ml of ethyl acetate and 15 ml of water containing potassium carbonate 0.18 g (1.31 mmol) and 2-ethyl aminobenzoic acid 0.1 ml (0.66 mmol) was dropwise-added under ice cooling to this, and it was stirred at room temperature for 20 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water, 1N-hydrochloric acid, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation. It was purified by silica gel column chromatography, and title compound 0.10 g (yield 29.4 %) were obtained.

(0091)

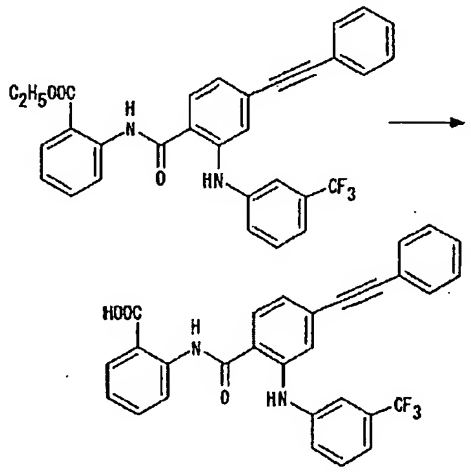
NMR (DMSO-d6) delta: 1.44 (3H, t, J = 7 Hz), 4.43 (2H, q, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1 Hz), 7.15 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.27-7.30 (1H, m), 7.33-7.37 (3H, m), 7.42-7.54 (6H, m), 7.61 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.81 (1H, d, J = 8 Hz), 8.12 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 9.83 (1H, s), 12.05 (1H, s).

(0092)

Example 9

2-(4-phenyl-ethynyl-2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid.

(0093)



(0094)

1N-sodium hydroxide solution 10 ml were added to ethanol (10 ml) solution of 2-(4-phenyl-ethynyl-2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester 100 mg (0.15 mmol) produced in Reference Example 4, and the mixture was heated under reflux for two hours. Ethanol was eliminated by distillation under reduced pressure, and the residue was neutralised at concentrated hydrochloric acid, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised at acetonitrile, and perform, title compound 75 mg (yield 77.6 %) were obtained.

(0095)

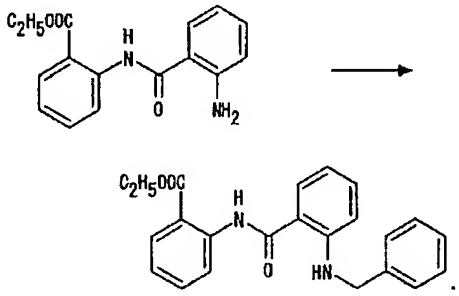
NMR (DMSO-d6) delta: 7.17-7.28 (3H, m), 7.38-7.54 (7H, m), 7.54-7.65 (3H, m), 7.82 (1H, d, J = 8 Hz), 8.01 (1H, dd, J = 8 Hz, 1 Hz), 8.55 (1H, d, J = 8 Hz), 9.28 (1H, s), 12.06 (1H, s).
IR (v, cm-1, KBr): 3304, 3500-2400, 1654, 1608, 1538, 1418, 1334, 1256, 1226, 1128,754.
EI-MS (m/z, %): 484 (M+, 12), 483 (34), 482 (100), 464 (12), 363 (12), 256 (27), 213 (13).
mp: 228-230 degrees.

(0096)

Reference Example 5

2-(2-benzylamino benzamide) benzoic acid ethyl ester.

(0097)



(0098)

Potassium carbonate 0.76 g (5.54 mmol) and benzyl bromide 0.6 ml (5.54 mmol) were added to N, N-dimethylformamide (20 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.5 g (5.28 mmol), and the mixture was stirred at room temperature for 18 hours. Water was added to the

reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 968 mg (yield 49.0 %) were obtained.

(0099)

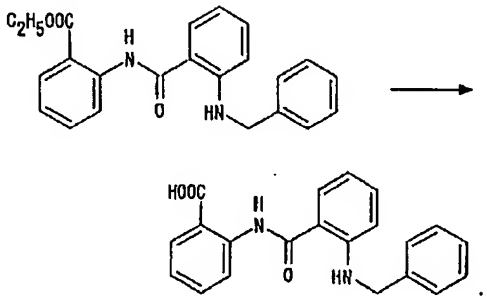
NMR (CDCl3) delta: 1.43 (3H, t, J = 7 Hz), 4.41 (2H, q, J = 7 Hz), 4.46 (2H, d, J = 6 Hz), 6.67 (1H, d, J = 8 Hz), 6.92 (1H, dt, J = 7 Hz, 1 Hz), 7.10 (1H, dt, J = 7 Hz, 1 Hz), 7.22-7.41 (6H, m), 7.57 (1H, dt, J = 8 Hz, 1 Hz), 7.78 (1H, dd, J = 8 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.30-8.43 (1H, m), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0100)

Example 10

2-(2-benzylamino benzamide) benzoic acid.

(0101)



(0102)

1N-sodium hydroxide solution 15 ml were added to 2-(2-benzylamino benzamide) benzoic acid ethyl ester 400 mg (1.07 mmol) ethanol solution (15 ml) produced in Reference Example 5, and the mixture was heated under reflux for three hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation. The residue was recrystallised using ether / hexane, and title compound 273 mg (yield 73.7 %) were obtained.

(0103)

NMR (CDCl3) delta: 4.47 (2H, s), 6.66-6.72 (2H, m), 7.14 (1H, dt, J = 8 Hz, 1 Hz), 7.22-7.41 (7H, m), 7.64 (1H, dt, J = 8 Hz, 1 Hz), 7.73 (1H, dd, J = 8 Hz, 1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, dd, J = 8 Hz, 1 Hz), 11.63 (1H, s).

IR (ν, cm-1, KBr): 3404, 3500-2800, 1698, 1644, 1610, 1516, 1452, 1362, 1212,756.

EI-MS (m/z, %): 346 (M+, 80), 328 (19), 210 (79), 209 (80), 181 (80), 180 (90), 91 (100).

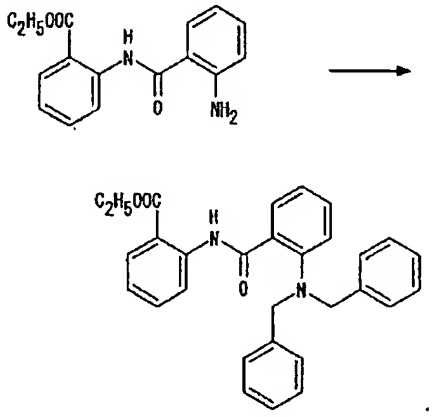
mp: 175-176 degrees.

(0104)

Reference Example 6

2-(2-dibenzylamino benzamide) benzoic acid ethyl ester.

(0105)



(0106)

Potassium carbonate 1.52 g (11.08 mmol) and benzyl bromide 1.3 ml (11.08 mmol) were added to N, N-dimethylformamide (20 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.5 g (5.28 mmol), and the mixture was stirred at room temperature for 18 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 1.08 mg (yield 44.0 %) were obtained.

(0107)

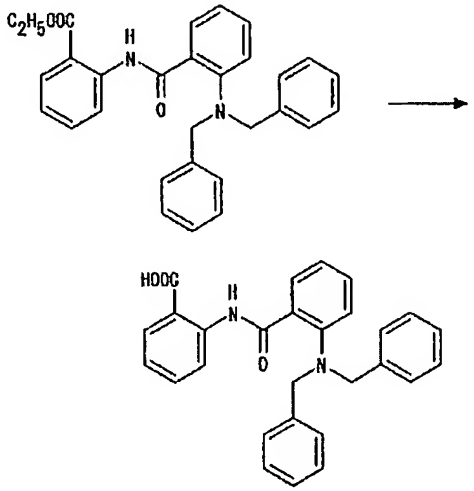
NMR (CDCl3) delta: 1.33 (3H, t, J = 7 Hz), 4.28 (2H, q, J = 7 Hz), 4.29 (4H, s), 6.87 (1H, dd, J = 8 Hz, 1 Hz), 7.06 (1H, dt, J = 8 Hz, 1 Hz), 7.11-1.21 (11H, m), 7.58 (1H, dd, J = 8 Hz, 1 Hz), 7.74 (1H, dd, J = 8 Hz, 1 Hz), 8.07 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, dd, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0108)

Example 11

2-(2-dibenzylamino benzamide) benzoic acid.

(0109)



(0110)

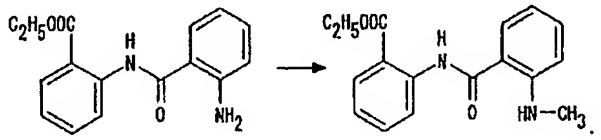
1N-sodium hydroxide solution 10 ml were added to 2-(2-dibenzylamino benzamide) benzoic acid ethyl ester 750 mg (1.61 mmol) ethanol solution (10 ml) produced in Reference Example 6, and the mixture was heated under reflux for three hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was distilled under reduced pressure. The residue was recrystallised using ethyl acetate / hexane, and title compound 590 mg (yield 84.0 %) were obtained.

(0111)

NMR (CDCl3) delta: 4.27 (4H, s), 6.86 (1H, dd, J = 8 Hz, 1 Hz), 7.07 (1H, dt, J = 8 Hz, 1 Hz), 7.11-7.22 (10H, m), 7.63 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.80 (1H, dd, J = 8 Hz, 1 Hz), 8.06 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.08 (1H, s).
IR (ν, cm-1, KBr): 3500-2700, 1718, 1636, 1506, 1452, 1288, 1180, 1164,762,698.
EI-MS (m/z, %): 436 (M+, 1), 435 (4), 346 (24), 345 (86), 327 (18), 209 (37), 208 (100), 91 (80).
mp: 147-148 degrees.

(0112)
Reference Example 7
2-(methylaminobenzamide) benzoic acid ethyl ester.

(0113)



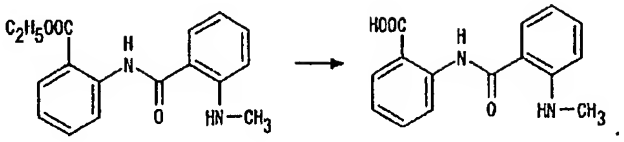
(0114)
Potassium carbonate 0.5 g (3.70 mmol) and iodomethane 0.3 ml (3.70 mmol) were added to N, N-dimethylformamide (10 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.0 g (3.52 mmol), and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 310 mg (yield 29.5 %) were obtained.

(0115)
NMR (CDCl3) delta: 1.42 (3H, t, J = 7 Hz), 2.91 (3H, d, J = 5 Hz), 4.41 (2H, q, J = 7 Hz), 6.69-6.74 (2H, m), 7.09 (1H, dt, J = 8 Hz, 1 Hz), 7.38 (1H, dt, J = 8 Hz, 1 Hz), 7.57 (1H, dt, J = 8 Hz, 1 Hz), 7.75 (1H, dd, J = 8 Hz, 1 Hz), 7.82 (1H, s), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.84 (1H, s).

(0116)
Example 12

2-(2-methylaminobenzamide) benzoic acid.

(0117)



(0118)

1N-sodium hydroxide solution 6 ml were added to 2-(2-methylaminobenzamide) benzoic acid ethyl ester 95 mg (0.32 mmol) ethanol solution (6 ml) produced in Reference Example 7, and the mixture was heated under reflux for one hour. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was distilled under reduced pressure. The residue was recrystallised using ether / hexane, and title compound 80 mg (yield 93.1 %) were obtained.

(0119)

NMR (CDCl3) delta: 2.83 (3H, s), 6.67 (1H, dt, J = 8 Hz, 1 Hz), 7.18 (1H, dt, J = 8 Hz, 1 Hz), 7.40 (1H, dt, J = 8 Hz, 1 Hz), 7.60-7.70 (3H, m), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.62 (1H, dd, J = 8 Hz, 1 Hz), 11.96 (1H, s), 13.71 (1H, br-s).

IR (v, cm-1, KBr): 3424, 3400-2500, 1690, 1642, 1608, 1522, 1452, 1296, 1214,752.

EI-MS (m/z, %): 270 (M+, 60), 252 (6), 134 (100), 105 (16), 91 (30), 77 (33).

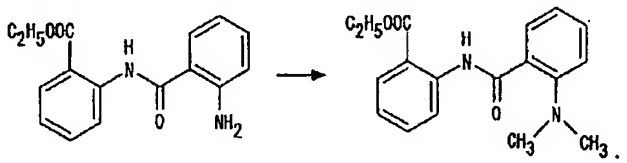
mp: 205-207 degrees.

(0120)

Reference Example 8

2-(dimethylamino benzamide) benzoic acid ethyl ester.

(0121)



(0122)

Potassium carbonate 1.0 g (7.04 mmol) and iodomethane 0.6 ml (7.04 mmol) were added to N, N-dimethylformamide (10 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.0 g (3.52 mmol), and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 710 mg (yield 64.6 %) were obtained.

(0123)

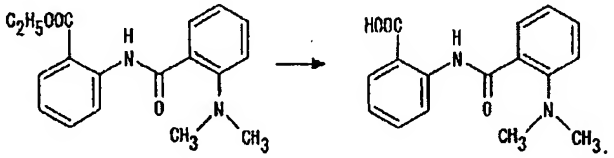
NMR (CDCl3) delta: 1.39 (3H, t, J = 7 Hz), 2.82 (6H, s), 4.35 (2H, q, J = 7 Hz), 7.06-7.12 (2H, m), 7.15 (1H, dd, J = 8 Hz, 1 Hz), 7.42 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.56 (1H, dd, J = 8 Hz, 1 Hz), 7.96 (1H, dd, J = 8 Hz, 1 Hz), 8.02 (1H, dd, J = 8 Hz, 1 Hz), 8.93 (1H, dd, J = 8 Hz, 1 Hz), 12.60 (1H, s).

(0124)

Example 13

2-(2-dimethylamino benzamide) benzoic acid.

(0125)



(0126)

1N-sodium hydroxide solution 10 ml were added to 2-(2-dimethylamino benzamide) benzoic acid ethyl ester 484 mg (1.55 mmol) ethanol solution (10 ml) produced in Reference Example 8, and the mixture was heated under reflux for two hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

distilled under reduced pressure. The residue was recrystallised using ether / hexane, and title compound 337 mg (yield 76.5 %) were obtained.

(0127)

NMR (CDCl3) delta: 4.27 (4H, s), 7.09-7.18 (3H, m), 7.44 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, dt, J = 8 Hz, 1 Hz), 7.99 (1H, dd, J = 7 Hz, 1 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.97 (1H, dd, J = 8 Hz, 1 Hz).

IR (ν, cm-1, KBr): 3400-2400, 1716, 1636, 1580, 1512, 1450, 1378, 1208,770,758.

EI-MS (m/z, %): 284 (M+, 15), 270 (3), 148 (100), 147 (88), 105 (16), 91 (24), 77 (19).

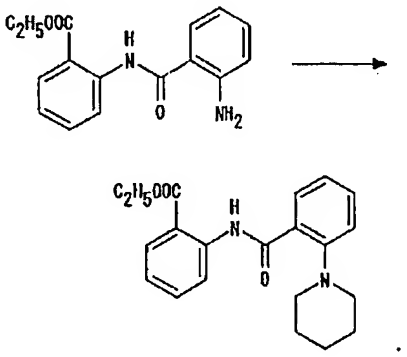
mp: 137-138 degrees.

(0128)

Reference Example 9

2-(2-piperidyl benzamide) benzoic acid ethyl ester.

(0129)



(0130)

Potassium carbonate 510 mg (3.69 mmol) and 1,5-diiodo pentane 0.3 ml (2.11 mmol) were added to N, N-dimethylformamide (15 ml) solution of 2-amino benzamide benzoic acid ethyl ester 500 mg (1.76 mmol), and the mixture was stirred at 60 degC for 20 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 75 mg (yield 12.1 %) were obtained.

(0131)

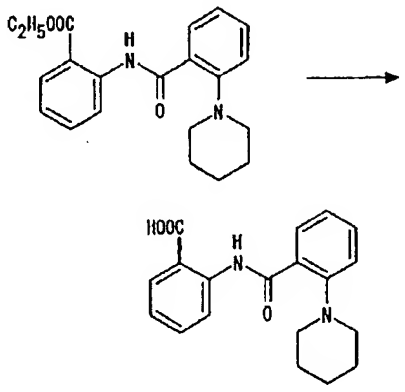
NMR (CDCl3) delta: 1.36 (3H, t, J = 7 Hz), 1.42-1.50 (2H, m), 1.56-1.67 (4H, m), 3.03 (4H, t, J = 5 Hz), 4.32 (2H, q, J = 7 Hz), 7.05-7.14 (3H, m), 7.41 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.57 (1H, dt, J = 8 Hz, 1 Hz), 7.86 (1H, dd, J = 8 Hz, 1 Hz), 8.06 (1H, dd, J = 8 Hz, 1 Hz), 8.84 (1H, d, J = 8 Hz), 12.29 (1H, s).

(0132)

Example 14

2-(2-piperidyl benzamide) benzoic acid.

(0133)



(0134)

1N-sodium hydroxide solution 10 ml were added to 2-(2-piperidyl benzamide) benzoic acid ethyl ester 75 mg (0.21 mmol) ethanol solution (10 ml) produced in Reference Example 9, and the mixture was heated under reflux for two hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was distilled under reduced pressure. The residue was recrystallised using ethyl acetate / hexane, and title compound 57 mg (yield 76.5 %) were obtained.

(0135)

NMR (CDCl3) delta: 1.43-1.50 (2H, m), 1.50-1.65 (4H, m), 2.88-3.08 (4H, m), 7.08-7.20 (3H, m), 7.44 (1H, dt, J = 8 Hz, 1 Hz), 7.61 (1H, dt, J = 8 Hz, 1 Hz), 7.91 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, d, J = 8 Hz).
IR (v, cm-1, KBr): 3400-2100, 1676, 1576, 1520, 1452, 1418, 1270, 908,766,756.
EI-MS (m/z, %): 324 (M+, 15), 188 (90), 187 (100), 159 (36).
mp: 192-193 degrees.

(0136)
Reference Example 10
2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0137)
Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 2-chloro-4-phenyl-ethynyl benzoic acid 0.82 g (3.19 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate 10 ml, and this was dropwise-added under ice cooling to mixed solution of 5 ml of ethyl acetate and 15 ml of water containing potassium carbonate 0.88 g (6.39 mmol) and 2-ethyl aminobenzoic acid 0.47 ml (3.19 mmol) and it was stirred at room temperature for three hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 1.08 g (yield 83.8 %) were obtained.

(0138)
NMR (CDCl3) delta: 1.40 (3H, t, J = 7 Hz), 4.37 (2H, q, J = 7 Hz), 7.16 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.35-7.41 (3H, m), 7.39-7.58 (3H, m), 7.59-7.66 (3H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.89 (1H, d, J = 8 Hz), 11.62 (1H, s).

(0139)
Reference Example 11
2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid.

(0140)

1M-sodium hydroxide solution 20 ml were added to ethanol (20 ml) solution of benzoic acid ethyl ester 1.03 g (2.55 mmol) produced in Reference Example 10, and it was heated with stirring for one hour, and next ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was added to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with ethanol, and title compound 0.82 g (yield 86.0 %) were obtained.

(0141)
NMR (DMSO-d6) delta: 7.26 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.45-7.50 (3H, m), 7.59-7.65 (2H, m), 7.66-7.72 (2H, m), 7.77 (1H, d, J = 8 Hz), 7.83 (1H, d, J = 1 Hz), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.57 (1H, d, J = 8 Hz), 11.67 (1H, s).

(0142)
Example 15
2-(2-hexyl amino-4-phenyl-ethynyl benzamide) benzoic acid.

(0143)
Potassium carbonate 140 mg (0.96 mmol) and 5 wt.% activated copper was added to hexylamine (5 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 300 mg (0.80 mmol) produced in Reference Example 10, and it was heated with stirring at 170 degrees in sealed tube for three hours, and next it was cooled to room temperature, and hexylamine was eliminated by distillation under reduced pressure. 1M-hydrochloric acid was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.12 g (yield 33.0 %) were obtained.

(0144)
NMR (CDCl3) delta: 0.91 (3H, t, J = 7 Hz), 1.28-1.40 (4H, m), 1.40-1.50 (2H, m), 1.68-1.76 (2H, m), 3.20 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1 Hz), 7.14 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.34-7.39 (3H, m), 7.54-7.60 (2H, m), 7.60-7.69 (2H, m), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.64 (1H, s).

IR (ν, cm-1, KBr): 3344, 2932, 1652, 1604, 1532, 1252,762,754.
EI-MS (m/z, %): 440 (m +,100), 422 (19), 369 (29), 304 (34), 232 (96).
mp: 211-213 degrees.

(0145)
Example 16
2-(2-benzylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0146)
Potassium carbonate 0.12 g (0.84 mmol) and 5 wt.% activated copper was added to benzylamine (3 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 260 mg (0.70 mmol) produced in Reference Example 10, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 90 mg (yield 28.7 %) were obtained.

(0147)
NMR (CDCl3) delta: 4.74 (2H, s), 6.85-6.90 (2H, m), 7.12-7.17 (1H, m), 7.26-7.30 (1H, m), 7.32-7.42 (6H, m), 7.50-7.55 (2H, m), 7.64 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.71 (1H, d, J = 8 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.79 (1H, dd, J = 8 Hz, 1 Hz), 11.71 (1H, s).
IR (ν, cm-1, KBr): 3240, 1682, 1650, 1604, 1538, 1266,766,756.
EI-MS (m/z, %): 446 (m +,100), 428 (37), 310 (84), 280 (87), 221 (42), 193 (69), 91 (22).
mp: 226-228 degrees.

(0148)
Reference Example 12
2-(2-methylpropyl) aminobenzoic acid.

(0149)
Potassium carbonate 1.06 g (7.16 mmol) and 5 wt.% activated copper was added to 2-methylpropyl amine (3 ml) solution of 2-chlorobenzoic acid 1.0 g (6.39 mmol), and it was heated with stirring at 170 degrees in sealed tube for one hour and next was cooled to room temperature. 1M-hydrochloric

acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.99 g (yield 88.0 %) were obtained.

(0150)

NMR (CDCl3) delta: 1.03 (6H, d, J = 7 Hz), 1.99 (1H, sept, J = 7 Hz), 3.04 (2H, d, J = 7 Hz), 6.56 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.68 (1H, dd, J = 8 Hz, 1 Hz), 7.38 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.98 (1H, dd, J = 8 Hz, 1 Hz).

(0151)

Example 17

2-(2-(2-methylpropyl amino) benzamide) benzoic acid.

(0152)

Thionyl chloride 0.5 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (5 ml) of 2-(2-methylpropyl) aminobenzoic acid 0.30 g (1.55 mmol) produced in Reference Example 12 and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and under a nitrogen atmosphere, to triethylamine 0.64 ml (4.66 mmol) and methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.21 g (1.55 mmol), it was dropwise-added under ice cooling, and this was stirred at room temperature for 18 hours. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.23 g (yield 46.9 %) were obtained.

(0153)

NMR (CDCl3) delta: 1.06 (6H, d, J = 7 Hz), 2.02 (1H, se pt, J = 7 Hz), 3.05 (2H, d, J = 7 Hz), 6.69 (1H, dt, J = 8 Hz, 1 Hz), 6.76 (1H, d, J = 8 Hz), 7.16 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.38 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.67 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.72 (1H, dd, J = 8 Hz, 1 Hz), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.84 (1H, dd, J = 8 Hz, 1 Hz), 11.57 (1H, s).

IR (v, cm-1, KBr): 2962, 1658, 1602, 1576, 1532, 1256,752,738.

EI-MS (m/z, %): 312 (m +,41), 269 (61), 251 (16), 132 (100), 120 (30).
mp: 159-160 degrees.

(0154)
Reference Example 13
2-cyclohexyl aminobenzoic acid.

(0155)
Potassium carbonate 1.06 g (7.16 mmol) and 5 wt.% activated copper was added to cyclohexylamine (3 ml) solution of 2-chlorobenzoic acid 1.0 g (6.39 mmol), and it was heated with stirring at 170 degrees in sealed tube for 30 minutes and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 1.27 g (yield 90.6 %) were obtained.

(0156)
NMR (CDCl3) delta: 1.34-1.47 (5H, m), 1.60-1.68 (1H, m), 1.74-1.83 (2H, m), 1.98-2.10 (2H, m), 3.36-3.46 (1H, m), 6.56 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.71 (1H, d, J = 8 Hz), 7.36 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.96 (1H, dd, J = 8 Hz, 1 Hz).

(0157)
Example 18
2-(2-(cyclohexyl amino) benzamide) benzoic acid.

(0158)
Thionyl chloride 0.5 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 2-cyclohexyl aminobenzoic acid 0.30 g (1.55 mmol) produced in Reference Example 13 and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and this was dropwise-added under ice cooling under a nitrogen atmosphere to triethylamine 0.57 ml (4.11 mmol) and methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.19 g (1.37 mmol), and it was stirred at room temperature for 18 hours. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was

washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.30 g (yield 59.3 %) were obtained.

(0159)
NMR (CDCl3) delta: 1.26-1.40 (3H, m), 1.40-1.52 (2H, m), 1.58-1.68 (1H, m), 1.72-1.84 (2H, m), 1.99-2.05 (2H, m), 3.44-3.54 (1H, m), 6.63 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.85 (1H, d, J = 8 Hz), 7.19 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.34 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.67 (1H, dd, J = 8 Hz, 1 Hz), 7.74 (1H, dd, J = 8 Hz, 1 Hz), 8.86 (1H, dd, J = 8 Hz, 1 Hz), 12.07 (1H, s).
IR (v, cm-1, KBr): 2936, 1658, 1574, 1532, 1252,754,740.
EI-MS (m/z, %): 338 (m +,100), 326 (5), 295 (22), 202 (18), 201 (16), 158 (41), 132 (19), 120 (19).
mp: 230-232 degrees.

(0160)
Reference Example 14
2-(2-chlorobenzamide) benzoic acid ethyl ester.

(0161)
Thionyl chloride 2.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (30 ml) of 2-chlorobenzoic acid 3.0 g (19.2 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 15 ml of ethyl acetate and 30 ml of water containing potassium carbonate 5.3 g (38.3 mmol) and 2-ethyl aminobenzoic acid 2.8 ml (19.2 mmol) and it was stirred at room temperature for three hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ether-hexane, and title compound 5.2 g (yield 89.7 %) were obtained.

(0162)
NMR (CDCl3) delta: 1.39 (3H, t, J = 7 Hz), 4.36 (2H, J = 7 Hz), 7.16 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.34-7.43 (2H, m), 7.45-7.49 (1H, m), 7.61 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.66 (1H, dd, J = 8 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.90 (1H, d, J = 8 Hz) 11.55 (1H, s).

(0163)

Reference Example 15

2-(2-chlorobenzamide) benzoic acid.

(0164)

1M-sodium hydroxide solution 50 ml were added to ethanol (50 ml) solution of (2-chlorobenzamide) benzoic acid ethyl ester 5.22 g (17.2 mmol) and were heated under reflux for three hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 4.15 g (yield 87.6 %) were obtained.

(0165)

NMR (DMSO-d6) delta: 7.22 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.49 (1H, ddd, J = 7.7 Hz, 1 Hz), 7.55 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.58-7.68 (2H, m), 7.70 (1H, dd, J = 7.1 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.60 (1H, d, J = 8 Hz), 11.95 (1H, s).

(0166)

Example 19

2-(2-hexyl amino benzamide) benzoic acid.

(0167)

Potassium carbonate 240 mg (1.74 mmol) and 5 wt.% activated copper was added to hexylamine (6 ml) solution of 2-(2-chlorobenzamide) benzoic acid 400 mg (1.45 mmol) produced in Reference Example 15 and it was heated with stirring at 170 degrees in sealed tube for one hour 30 minutes and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 370 mg (yield 75.8 %) were obtained.

(0168)

NMR (CDCl3) delta: 0.90 (3H, t, J = 7 Hz), 1.28-1.50 (6H, m), 1.64-1.74 (2H, m), 3.19 (2H, t, J = 7 Hz), 6.67 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.74 (1H, d, J = 8 Hz), 7.14 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.36 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.68 (1H, dd, J = 8 Hz, 1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.52 (1H, s).

IR (ν, cm-1, KBr): 2924, 2856, 1698, 1646, 1612, 1574, 1538, 1294, 1222,756,740.

EI-MS (m/z, %): 340 (m +,94), 322 (13), 269 (75), 251 (26), 204 (32), 132 (100), 120 (30).

mp: 151-152 degrees.

(0169)

Example 20

2-(2-(2,2-dimethylpropyl amino) benzamide) benzoic acid.

(0170)

Potassium carbonate 240 mg (1.74 mmol) and 5 wt.% activated copper was added to 2,2-dimethylpropyl amine (7 ml) solution of 2-(2-chlorobenzamide) benzoic acid 400 mg (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ether-hexane, and title compound 170 mg (yield 36.3 %) were obtained.

(0171)

NMR (CDCl3) delta: 1.06 (9H, m), 2.99 (2H, s), 6.64 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.13 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.34 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.70 (1H, dd, J = 8 Hz, 1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, dd, J = 8 Hz, 1 Hz), 11.57 (1H, s).

IR (ν, cm-1, KBr): 3368, 2960, 1666, 1578, 1526, 1262,758,746.

EI-MS (m/z, %): 326 (m +,47), 269 (89), 251 (22), 132 (100), 120 (23).

mp: 193-194 degrees.

(0172)

Example 21

2-(2-octyl amino benzamide) benzoic acid.

(0173)
Potassium carbonate 0.24 g (1.74 mmol) and 5 wt.% activated copper was added to octyl amine (4 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.40 g (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.25 g (yield 45.9 %) were obtained.

(0174)
NMR (CDCl3) delta: 0.89 (3H, t, J = 7 Hz), 1.24-1.39 (8H, m), 1.39-1.49 (2H, m), 1.65-1.75 (2H, m), 3.19 (2H, t, J = 7 Hz), 6.67 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.75 (1H, d, J = 8 Hz), 7.14 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.36 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.69 (1H, dd, J = 8 Hz, 1 Hz), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.67 (1H, s).
IR (ν, cm-1, KBr): 3228, 2928, 2852, 1698, 1646, 1610, 1574, 1540, 1292, 1204,756,738.
EI-MS (m/z, %): 368 (m +,90), 340 (25), 269 (96), 251 (22), 132 (100), 120 (30).
mp: 146-147 degrees.

(0175)
Example 22
2-(2-decyl amino benzamide) benzoic acid.

(0176)
Potassium carbonate 240 mg (1.74 mmol) and 5 wt.% activated copper was added to decyl amine (4 ml) solution of 2-(2-chlorobenzamide) benzoic acid 400 mg (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by

silica gel chromatography, and thereafter, it was recrystallised with acetonitrile, and title compound 300 mg (yield 51.9 %) were obtained.

(0177)

NMR (CDCl3) delta: 0.88 (3H, t, J = 7 Hz), 1.20-1.38 (12H, m), 1.38-1.48 (2H, m), 1.65-1.74 (2H, m), 3.18 (2H, t, J = 7 Hz), 6.66 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.75 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.35 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.69 (1H, dd, J = 8 Hz, 1 Hz), 8.15 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.58 (1H, s).

IR (v, cm-1, KBr): 3326, 2924, 2852, 1698, 1646, 1610, 1574, 1540, 1294, 1200,756,736.

EI-MS (m/z, %): 396 (m +,74), 368 (28), 340(11), 269 (100), 251 (26), 132 (78), 120 (30).

mp: 126-127 degrees.

(0178)

Reference Example 16

2-(2-iso indolyl benzamide) benzoic acid ethyl ester.

(0179)

Potassium carbonate 530 mg (3.87 mmol) and alpha, alpha'-dibromo-o-xylene 470 mg (1.76 mmol) were added to N, N-dimethylformamide (5 ml) solution of 2-(2-amino benzamide) benzoic acid ethyl ester 500 mg (1.76 mmol), and it was heated with stirring at 110 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid solution was added to the reaction solution and was extracted with acetic acid ethyl ester. The organic layer was washed with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 360 mg (yield 53.1 %) were obtained.

(0180)

NMR (CDCl3) delta: 1.31 (3H, t, J = 7 Hz), 4.22 (2H, q, J = 7 Hz), 4.75 (4H, m), 6.88 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.97 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.58-7.65 (2H, m), 8.05 (1H, dd, J = 8 Hz, 1 Hz), 8.95 (1H, d, J = 8 Hz), 11.66 (1H, s).

(0181)

Example 23

2-(2-iso indolyl benzamide) benzoic acid.

(0182)

1M-sodium hydroxide solution (5 ml) was added to ethanol (5 ml) solution of 2-(2-iso indolyl benzamide) benzoic acid ethyl ester 360 mg (0.93 mmol) produced in Reference Example 16 and was heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. To the residue, concentrated hydrochloric acid was dropwise-added under ice cooling, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 260 mg (yield 77.7 %) were obtained.

(0183)

NMR (CDCl3) delta: 4.71 (4H, s), 6.90 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.99 (1H, d, J = 8 Hz), 7.13-7.23 (5H, m), 7.40 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.63 (1H, dd, J = 7.1 Hz), 7.67 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.08 (1H, dd, J = 8 Hz, 1 Hz), 8.97 (1H, d, J = 8 Hz), 11.48 (1H, s).
IR (ν, cm-1, KBr): 3328, 1668, 1518, 1264,756.
EI-MS (m/z, %): 358 (m +,15), 312 (7), 269 (10), 221 (52), 193 (100), 132 (14).
mp: 185-186 degrees.

(0184)

Example 24
2-(2-(1-propyl butyl) amino benzamide) benzoic acid.

(0185)

Potassium carbonate 0.15 g (1.11 mmol) and 5 wt.% activated copper was added to 4-heptyl amine (3 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.26 g (0.93 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for five hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.15 g (yield 45.0 %) were obtained.

(0186)

NMR (CDCl3) delta: 0.92 (6H, t, J = 7 Hz), 1.30-1.62 (8H, m), 3.50 (1H, pent, J = 6 Hz), 6.61 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.75 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.32 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.68 (1H, dd, J = 8 Hz, 1 Hz), 8.79 (1H, dd, J = 8 Hz, 1 Hz), 11.55 (1H, s).
IR (ν, cm-1, KBr): 2956, 2928, 1652, 1602, 1578, 1532, 1256,752, 742.
EI-MS (m/z, %): 354 (m +,22), 311 (75), 293 (6), 174 (100), 146 (19), 132 (13).
mp: 139-140 degrees.

(0187)
Example 25
2-(2-(1-methyl hexyl) amino benzamide) benzoic acid

(0188)
Potassium carbonate 0.21 g (1.52 mmol) and 5 wt.% activated copper was added to 2-amino heptane (3 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.35 g (1.27 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for five hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from hexane, and title compound 0.23 g (yield 50.4 %) were obtained.

(0189)
NMR (CDCl3) delta: 0.88 (3H, t, J = 7 Hz), 1.24 (3H, d, J = 6 Hz), 1.26-1.56 (7H, m), 1.58-1.70 (1H, m), 3.56 (1H, q, J = 6 Hz), 6.63 (1H, dd, J = 7 Hz, 7 Hz), 6.74 (1H, d, J = 8 Hz), 7.10-7.16 (1H, m), 7.30-7.38 (1H, m), 7.60-7.66 (1H, m), 7.69 (1H, dd, J = 8 Hz, 1 Hz), 8.15 (1H, dd, J = 8 Hz, 1. Hz), 8.79 (1H, d, J = 8 Hz), 11.54 (1H, s).
IR (ν, cm-1, KBr): 2952, 2932, 1698, 1652, 1612, 1574, 1538, 1264, 756,742.
EI-MS (m/z, %): 354 (m +,22), 336 (4), 311 (28), 283 (67), 174 (100), 146 (19), 132 (13).
mp: 108-109 degrees.

(0190)
Example 26
2-(2-(2-ethylhexyl) amino benzamide) benzoic acid.

(0191)

(0192)

Potassium carbonate 0.24 g (1.74 mmol) and 5 wt.% activated copper was added to 2-ethylhexyl amine (3 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.40 g (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.25 g (yield 47.4 %) were obtained.

(0193)

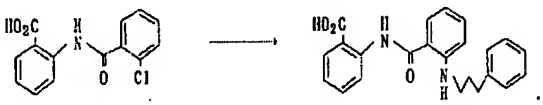
NMR (CDCl3) delta: 0.86-0.96 (6H, m), 1.26-1.54 (8H, m), 1.61-1.72 (1H, m), 3.09 (1H, dd, J = 12 Hz, 6 Hz), 3.11 (1H, dd, J = 12 Hz, 6 Hz), 6.63-6.68 (1H, m), 6.74 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.36 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.69 (1H, dd, J = 7.1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, dd, J = 8 Hz, 1 Hz), 11.55 (1H, s).
IR (ν, cm-1, KBr): 2960, 2924, 1654, 1602, 1530, 1256,788,746.
EI-MS (m/z, %): 368 (m +,23), 269 (70), 251 (18), 174 (3), 146 (5), 132 (100), 120 (28).
mp: 120-121 degrees.

(0194)

Example 27

2-(2-(3-phenylpropyl) amino benzamide) benzoic acid.

(0195)



(0196)

Potassium carbonate 0.18 g (1.31 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (3 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.30 g (1.09 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.18 g (yield 42.9 %) were obtained.

(0197)

NMR (CDCl3) delta: 1.98-2.08 (2H, m), 2.77 (2H, t, J = 7 Hz), 3.21 (2H, t, J = 7 Hz), 6.64-6.72 (2H, m), 7.10-7.24 (4H, m), 7.24-7.36 (3H, m), 7.61-7.67 (1H, m), 7.70 (1H, dd, J = 8 Hz, 1 Hz), 8.15 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, d, J = 8 Hz), 11.61 (1H, s).

IR (v, cm-1, KBr): 2920, 1650, 1602, 1574, 1534, 1262,758.

EI-MS (m/z, %): 374 (m +,51), 356 (3), 269 (69), 251 (22), 174 (5), 146 (14), 132 (100), 120 (36).

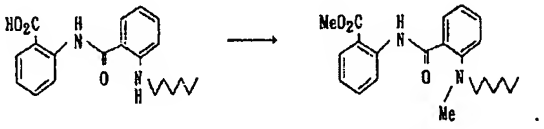
mp: 202-203 degrees.

(0198)

Reference Example 17

2-(2-(N-methyl hexyl amino) benzamide) methyl benzoate ester.

(0199)



(0200)

Potassium carbonate 0.13 g (0.97 mmol) and iodo methane 0.1 ml (1.76 mmol) were added to N, N-dimethylformamide (5 ml) solution of 2-(2-hexyl amino benzamide) benzoic acid 0.15 g (0.44 mmol) produced in Example 19, and the mixture was stirred at 50 degrees for 17 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.14 g (yield 85.7 %) were obtained.

(0201)

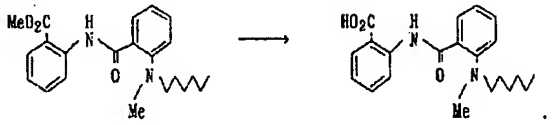
NMR (CDCl3) delta: 0.78 (3H, t, J = 7 Hz), 1.10-1.22 (6H, m), 1.40-1.50 (2H, m), 2.83 (3H, s), 2.97-3.04 (2H, m), 3.88 (3H, s), 7.07-7.14 (2H, m), 7.17 (1H, d, J = 8 Hz), 7.41 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.54-7.60 (1H, m), 7.98 (2H, ddd, J = 9.8,1 Hz), 8.86 (1H, d, J = 8 Hz), 12.58 (1H, s).

(0202)

Example 28

2-(2-(N methyl hexyl amino) benzamide) benzoic acid.

(0203)



(0204)

1M-sodium hydroxide solution 5 ml were added to ethanol (5 ml) solution of 2-(2-(N-methyl hexyl amino) benzamide) methyl benzoate 0.14 g (0.38 mmol) produced in Reference Example 17 and were heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.09 g (yield 68.1 %) were obtained.

(0205)

NMR (CDCl3) delta: 0.71-0.77 (3H, m), 1.05-1.15 (6H, m), 1.38-1.50 (2H, m), 2.78 (3H, s), 2.92-3.00 (2H, m), 7.08-7.18 (3H, m), 7.38-7.66 (1H, m), 7.98 (1H, dd, J = 8 Hz, 1 Hz), 8.08 (1H, dd, J = J = 8 Hz, 1 Hz), 8.87 (1H, d, J = 8 Hz).

IR (ν, cm-1, KBr): 2928, 1664, 1586, 1516, 1234,756.

EI-MS (m/z, %): 354 (m +,22), 283 (42), 265 (46), 218 (69), 217 (93), 146 (46), 134 (100), 132 (67).

(0206)

Reference Example 18

2-(2,6-dichlorobenzamide) benzoic acid ethyl ester.

(0207)

(0208)

Thionyl chloride 2.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (20 ml) of 2,6-dichloro benzoic acid 3.0 g (15.7 mmol) and were heated under reflux for two hours, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 20 ml of ethyl acetate and 30 ml of water containing potassium carbonate 4.3 g (31.4 mmol) and 2-ethyl aminobenzoic acid 2.3 ml (15.7 mmol) and it was stirred at room temperature for 42 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 2.8 g (yield 53.6 %) were obtained.

(0209)

NMR (CDCl3) delta: 1.39 (3H, t, J = 7 Hz), 4.34 (2H, J = 7 Hz), 7.16-7.22 (1H, m), 7.30 (1H, dd, J = 9 Hz, 2 Hz), 7.61-7.67 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.90 (1H, dd, J = 8 Hz, 1 Hz), 11.39 (1H, s).

(0210)

Reference Example 19

2-(2,6-dichlorobenzamide) benzoic acid.

(0211)

(0212)

1M-sodium hydroxide solution (20 ml) was added to ethanol (20 ml) solution of benzoic acid ethyl ester 2.82 g (8.34 mmol) produced in Reference Example 18, and it was heated under reflux for 6 hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 2.08 g (yield 80.3 %) were obtained.

(0213)

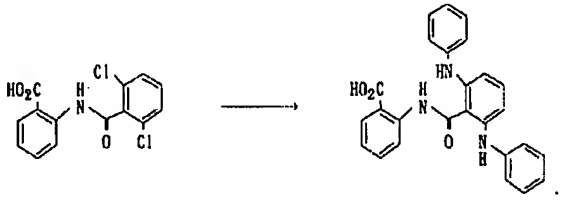
NMR (DMSO-d6) delta: 7.28 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.55 (1H, dd, J = 9 Hz, 7 Hz), 7.60-7.65 (2H, m), 7.70 (1H, ddd, J = 9 Hz, 8 Hz, 1 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.55 (1H, dd, J = 8 Hz, 1 Hz), 11.56 (1H, s).

(0214)

Example 29

2-(2,6-diphenylamino benzamide) benzoic acid.

(0215)



(0216)

Potassium carbonate 0.32 g (2.32 mmol) and 5 wt.% activated copper was added to aniline (3 ml) solution of 2-(2,6-dichlorobenzamide) benzoic acid 0.30 g (0.97 mmol) produced in Reference Example 19 and was heated under reflux for four hours and thereafter, was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel

chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.13 g (yield 30.8 %) were obtained.

(0217)

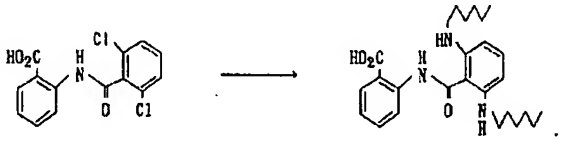
NMR (CDCl3) delta: 6.83 (2H, d, J = 8 Hz), 6.89-6.95 (2H, m), 7.06-7.16 (6H, m), 7.20-7.28 (4H, m), 7.53-7.59 (1H, m), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.72 (1H, d, J = 8 Hz), 11.53 (1H, s).
IR (ν, cm-1, KBr): 2960, 1680, 1658, 1574, 1508, 1262,752.
EI-MS (m/z, %): 439 (m +,57), 421 (10), 368 (8), 303 (23), 302 (22), 276 (73), 231 (52), 205 (100).
mp: 110-111 degrees.

(0218)

Example 30

2-(2,6-dihexyl amino benzamide) benzoic acid.

(0219)



(0220)

Potassium carbonate 0.32 g (2.32 mmol) and 5 wt.% activated copper was added to hexylamine (3 ml) solution of 2-(2,6-dichlorobenzamide) benzoic acid 0.30 g (0.97 mmol) produced in Reference Example 19, and it was heated with stirring at 170 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ether-hexane, and title compound 0.21 g (yield 49.9 %) were obtained.

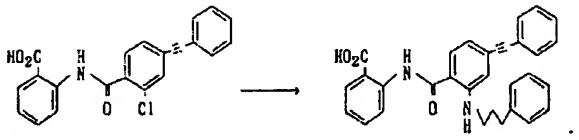
(0221)

NMR (CDCl3) delta: 0.82 (3H, t, J = 7 Hz), 1.19-1.39 (6H, m), 1.56-1.62 (2H, m), 3.08 (2H, t, J = 7 Hz), 6.10 (2H, d, J = 8 Hz), 7.09-7.17 (2H, m), 7.62 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, d, J = 8 Hz).

IR (ν, cm-1, KBr): 1682, 1646, 1580, 1520, 1270,748.
EI-MS (m/z, %): 423 (m +,27), 405 (13), 368 (100), 286 (42), 236 (45).
mp: 195-197 degrees.

(0222)
Example 31
2-(4-phenyl-ethynyl-2-(3-phenylpropyl amino) benzamide) benzoic acid.

(0223)



(0224)
Potassium carbonate 0.18 g (1.28 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (3 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 0.40 g (1.06 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with methanol, and title compound 0.30 g (yield 59.2 %) were obtained.

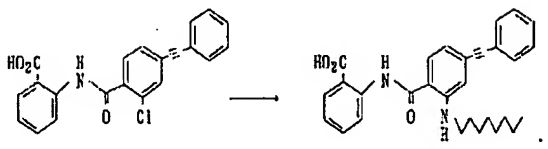
(0225)
NMR (CDCl3) delta: 2.06 (2H, pent, J = 7 Hz), 2.78 (2H, t, J = 7 Hz), 3.23 (2H, t, J = 7 Hz), 6.82-6.87 (2H, m), 7.13-7.32 (7H, m), 7.34-7.39 (3H, m), 7.54-7.58 (2H, m), 7.62-7.69 (2H, m), 8.18 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, d, J = 8 Hz), 11.62 (1H, s).
IR (ν, cm-1, KBr): 2936, 1650, 1604, 1586, 1538, 1260,754.
EI-MS (m/z, %): 474 (m +,80), 456 (57), 374 (20), 351 (50), 269 (23), 232 (100), 176 (27), 132 (41), 120 (22), 91 (72).
mp: 199-200 degrees.

(0226)

Example 32

2-(2-octyl amino-4-phenyl-ethynyl benzamide) benzoic acid.

(0227)



(0228)

Potassium carbonate 0.18 g (1.28 mmol) and 5 wt.% activated copper was added to octyl amine (3 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 0.40 g (1.06 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.05 g (yield 9.6 %) were obtained.

(0229)

NMR (CDCl3) delta: 0.88 (3H, t, J = 7 Hz), 1.22-1.40 (8H, m), 1.40-1.50 (2H, m), 1.78 (2H, pent, J = 7 Hz), 3.20 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1 Hz), 7.12-7.18 (1H, m), 7.34-7.40 (3H, m), 7.56-7.60 (2H, m), 7.63-7.69 (2H, m), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.59 (1H, s).

IR (ν, cm-1, KBr): 2924, 1656, 1604, 1564, 1520, 1254,752.

EI-MS (m/z, %): 450 (M-H8, 49), 421 (10), 368 (18), 351 (72), 176 (15).

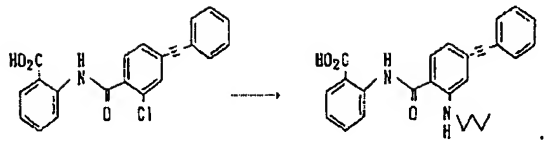
mp: 162-163 degrees.

(0230)

Example 33

2-(2-butylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0231)



(0232)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to butyl amine (2 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 018 g (yield 53.2 %) were obtained.

(0233)

NMR (CDCl3) delta: 0.98 (3H, t, J = 7 Hz), 1.44-1.54 (2H, m), 1.66-1.76 (2H, m), 3.02 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1 Hz), 7.12-7.18 (1H, m), 7.33-7.40 (3H, m), 7.54-7.60 (2H, m), 7.62-7.68 (2H, m), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.59 (1H, s).

IR (v, cm-1, KBr): 3438, 2956, 1680, 1650, 1540, 1262,754.

EI-MS (m/z, %): 412 (m +,69), 394 (12), 369 (22), 276 (33), 232 (100), 176 (23).

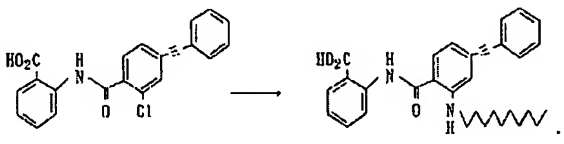
mp: 217-219 degrees.

(0234)

Example 34

2-(3-decyl amino-4-phenyl-ethynyl benzamide) benzoic acid.

(0235)



(0236)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to decyl amine (3 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.08 g (yield 18.9 %) were obtained.

(0237)

NMR (CDCl3) delta: 0.87 (3H, t, J = 7 Hz), 1.20-1.40 (12H, m), 1.40-1.50 (2H, m), 1.66-1.76 (2H, m), 3.20 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1), 7.12-7.18 (1H, m), 7.23-7.40 (3H, m), 7.53-7.59 (2H, m), 7.62-7.68 (2H, m), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.60 (1H, s).

IR (v, cm-1, KBr): 2924, 1652, 1608, 1538, 1258,764,754.

EI-MS (m/z, %): 496 (m +,42), 478 (87), 369 (26), 351 (100), 323 (30), 232 (45).

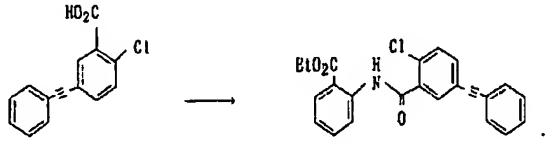
mp: 144-146 degrees.

(0238)

Reference Example 20

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0239)



(0240)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (15 ml) of 2-chloro-5-phenyl-ethynyl benzoic acid 2.0 g (7.79 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 10 ml of ethyl acetate and 15 ml of water containing

potassium carbonate 2.1 g (15.6 mmol) and ethyl aminobenzoic acid 1.1 ml (7.79 mmol) and it was stirred at room temperature for two hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.7 g (yield 53.4 %) were obtained.

(0241)

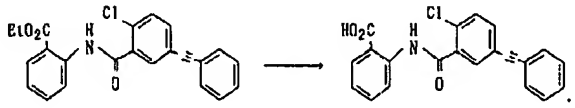
NMR (CDCl3) delta: 1.40 (3H, t, J = 7 Hz), 4.37 (2H, q, J = 7 Hz), 7.14-7.20 (1H, m), 7.33-7.38 (3H, m), 7.45 (1H, d, J = 8 Hz), 7.50-7.56 (3H, m), 7.60-7.66 (1H, m), 7.80 (1H, d, J = 2 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.88 (1H, d, J = 8 Hz), 11.57 (1H, s).

(0242)

Reference Example 21

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid.

(0243)



(0244)

1M-sodium hydroxide solution 20 ml were added to ethanol (15 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 1.68 g (4.16 mmol) produced in Reference Example 20 and were heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.53 g (yield 97.8 %) were obtained.

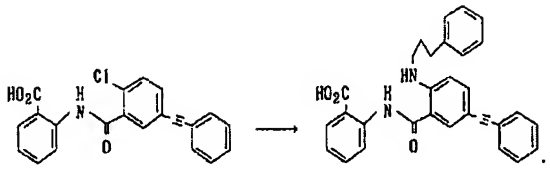
NMR (DMSO-d6) delta: 7.24-7.30 (1H, m), 7.43-7.48 (3H, m), 7.57-7.63 (2H, m), 7.65-7.74 (3H, m), 7.91 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.50 (1H, d, J = 8 Hz), 11.61 (1H, s), 13.71 (1H, br-s).

(0245)

Example 35

2-(5-phenyl-ethynyl-2-(3-phenylpropyl) amino benzamide) benzoic acid.

(0246)



(0247)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (1.5 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 21, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.15 g (yield 38.6 %) were obtained.

(0248)

NMR (CDCl3) delta: 2.00-2.09 (2H, m), 2.78 (2H, t, J = 7 Hz), 3.24 (2H, t, J = 7 Hz), 6.65 (1H, d, J = 8 Hz), 6.95-7.02 (1H, m), 7.17-7.33 (8H, m), 7.46-7.55 (3H, m), 7.58-7.64 (1H, m), 7.91 (1H, d, J = 2 Hz), 8.01 (1H, d, J = 8 Hz), 8.79 (1H, d, J = 8 Hz), 11.70 (1H, s).

IR (ν, cm-1, KBr): 2928, 1658, 1604, 1532, 1262,756.

EI-MS (m/z, %): 474 (m +,9), 456 (100), 383 (36), 351 (46), 232 (9).

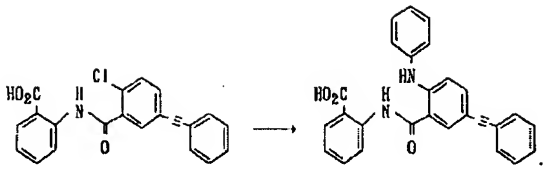
mp: 194-196 degrees.

(0249)

Example 36

2-(2-phenylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0250)



(0251)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (1.5 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 21, and it was heated with stirring at 180 degrees for one hour 30 minutes and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.17 g (yield 50.7 %) were obtained.

(0252)

NMR (CDCl3) delta: 6.99-7.04 (1H, m), 7.07-7.12 (1H, m), 7.22-7.39 (8H, m), 7.46 (1H, dd, J = 8 Hz, 2 Hz), 7.50-7.56 (2H, m), 7.61-7.66 (1H, m), 7.97 (1H, d, J = 2 Hz), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, d, J = 8 Hz), 9.81 (1H, s), 11.79 (1H, s).

IR (ν, cm-1, KBr): 1682, 1646, 1580, 1520, 1270,748.

El-MS (m/z, %): 423 (m +,27), 405 (13), 368 (100), 286 (42), 236 (45).

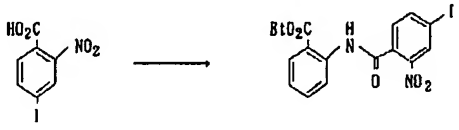
mp: 199-202 degrees.

(0253)

Reference Example 22

2-(4-iodo-2-nitrobenzamide) benzoic acid ethyl ester.

(0254)



(0255)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 4-iodo-2-nitrobenzoic acid 1.82 g (6.21 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (15 ml) and this was dropwise-added under ice cooling to mixed solution of 5 ml of ethyl acetate and 15 ml of water containing potassium carbonate 1.8 g (13.05 mmol) and 2-ethyl aminobenzoic acid 0.97 ml (6.52 mmol) and it was stirred at room temperature for 16 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 2.25 g (yield 82.3 %) were obtained.

(0256)

NMR (CDCl3) delta: 1.40 (3H, t, J = 7 Hz), 4.35 (2H, J = 7 Hz), 7.16-7.21 (1H, m), 7.44 (1H, d, J = 8 Hz), 7.59-7.65 (1H, m), 8.05-8.12 (2H, m), 8.39 (1H, d, J = 1 Hz), 8.77 (1H, d, J = 8 Hz), 11.66 (1H, s).

(0257)

Reference Example 23

2-(2-amino-4-iodo benzamide) benzoic acid ethyl ester.

(0258)

(0259)

20 % ammonium sulphide solution 10 ml were dropwise-added to ethanol (10 ml) solution of 2-(4-iodo-2-nitrobenzamide) benzoic acid ethyl ester 2.25 g (5.11 mmol) produced in Reference Example 22 and were heated under reflux for four hours. The reaction solution was cooled with ice, and unnecessary matter was filtered. 4M hydrochloric acid was added to filtrate, and it was acidified, and next extraction was carried out with ethyl acetate. The organic layer was washed successively at water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from methylene chloride, and title compound 0.97 g (yield 46.5 %) were obtained.

(0260)

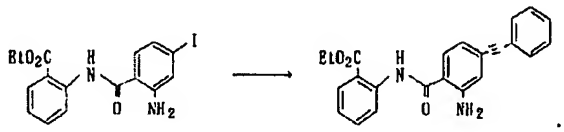
NMR (CDCl3) delta: 1.42 (3H, t, J = 7 Hz), 4.41 (2H, J = 7 Hz), 7.07-7.14 (3H, m), 7.41 (1H, d, J = 8 Hz), 7.58 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.77 (1H, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0261)

Reference Example 24

2-(2-amino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0262)



(0263)

Under a nitrogen atmosphere, phenyl acetylene 0.4 ml (3.55 mmol), dichlorobis triphenylphosphine palladium 0.02 g (0.02 mmol) and copper iodide 0.01 g (0.04 mmol) were added to diethylamine (10 ml) solution of 2-(2-amino-4-iodo benzamide) benzoic acid ethyl ester 0.97 g (2.36 mmol) produced in Reference Example 23, and the mixture was stirred at room temperature for one hour, and next diethylamine was eliminated by distillation under reduced pressure. 1M-hydrochloric acid was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from chloroform-hexane, and title compound 0.55 g (yield 60.9 %) were obtained.

(0264)

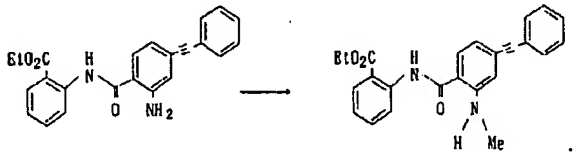
NMR (CDCl3) delta: 1.43 (3H, t, J = 7 Hz), 4.42 (2H, q, J = 7 Hz), 6.89 (1H, d, J = 1 Hz), 6.92 (1H, dd, J = 8 Hz, 1 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.34-7.38 (3H, m), 7.51-7.56 (2H, m), 7.69 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.70 (1H, d, J = 8 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.89 (1H, s).

(0265)

Reference Example 25

2-(2-methylamino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0266)



(0267)

Potassium carbonate 300 mg (2.24 mmol) and iodo methane 0.2 ml (3.36 mmol) were added to N, N-dimethylformamide (6 ml) solution of 2-(2-amino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.43 g (1.12 mmol) produced in Reference Example 24, and the mixture was stirred at room temperature for seven hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.24 g (yield 42.0 %) were obtained.

(0268)

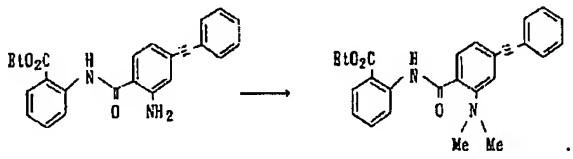
NMR (CDCl3) delta: 1.43 (3H, t, J = 7 Hz), 2.93 (3H, d, J = 3 Hz), 4.42 (2H, q, J = 7 Hz), 6.84-6.90 (2H, m), 7.08-7.14 (1H, m), 7.34-7.39 (3H, m), 7.54-7.61 (3H, m), 7.72 (1H, d, J = 8 Hz), 7.84-7.94 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.76 (1H, dd, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0269)

Reference Example 26

2-(2-dimethylamino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0270)



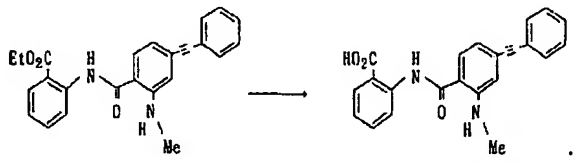
(0271)

Potassium carbonate 300 mg (2.24 mmol) and iodo methane 0.2 ml (3.36 mmol) were added to N, N-dimethylformamide (6 ml) solution of 2-(2-amino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.43 g (1.12 mmol) produced in Reference Example 24, and the mixture was stirred at room temperature for 17 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography with the residue, and title compound 0.29 g (yield 63.0 %) were obtained.

(0272)
NMR (CDCl3) delta: 1.39 (3H, t, J = 7 Hz), 2.84 (6H, s), 4.35 (2H, q, J = 7 Hz), 7.11 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.24-7.27 (1H, m), 7.30 (1H, d, J = 1 Hz), 7.34-7.40 (3H, m), 7.53-7.60 (3H, m), 7.94 (1H, d, J = 8 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.91-8.94 (1H, m), 12.59 (1H, s).

(0273)
Example 37
2-(2-methylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0274)



(0275)
1M-sodium hydroxide solution 15 ml were added to ethanol (10 ml) solution of 2-(2-methylamino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.06 g (0.16 mmol) produced in Reference Example 25 and were heated under reflux for four hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.05 g (yield 94.0 %) were obtained.

(0276)

NMR (CDCl3) delta: 2.94 (3H, s), 6.86 (1H, dd, J = 8 Hz, 1 Hz), 6.88 (1H, d, J = 1 Hz), 7.15 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.34-7.40 (3H, m), 7.54-7.59 (2H, m), 7.62-7.67 (1H, m), 7.66 (1H, d, J = 8 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.66 (1H, s).

IR (ν, cm-1, KBr): 3416, 1690, 1646, 1608, 1584, 1536, 1230,752.

EI-MS (m/z, %): 370 (m +,4), 352 (1), 278 (1), 256 (1), 234 (5).

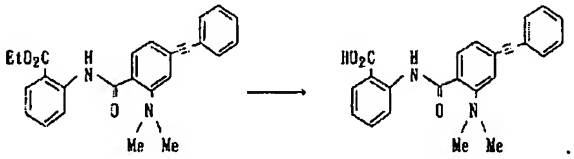
mp: 219-220 degrees.

(0277)

Example 38

2-(2-dimethylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0278)



(0279)

1M-sodium hydroxide solution 10 ml were added to ethanol (10 ml) solution of 2-(2-dimethylamino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.29 g (0.71 mmol) produced in Reference Example 26 and were heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from chloroform-hexane, and title compound 0.19 g (yield 69.4 %) were obtained.

(0280)

NMR (CDCl3) delta: 2.94 (6H, s), 7.13-7.19 (1H, m), 7.28 (1H, dd, J = 8 Hz, 1 Hz), 7.32 (1H, d, J = 1 Hz), 7.35-7.40 (3H, m), 7.54-7.60 (2H, m), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.96 (1H, d, J = 8 Hz), 8.12 (1H, dd, J = 8 Hz, 1 Hz), 8.97 (1H, d, J = 8 Hz), 12.4-12.6 (1H, m).

IR (ν, cm-1, KBr): 1696, 1652, 1586, 1522, 1196,764,752.

EI-MS (m/z, %): 384 (m +,19), 366 (3), 248 (100), 247 (90), 191 (13), 176(11) .

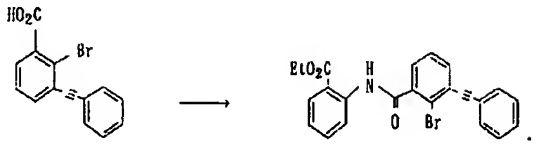
mp: 186-187 degrees.

(0281)

Reference Example 27

2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0282)



(0283)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 2-bromo-3-phenyl-ethynyl benzoic acid 1.53 g and were heated under reflux for 45 minutes, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 5 ml of ethyl acetate and 15 ml of water containing potassium carbonate 1.4 g (10.16 mmol) and 2-ethyl aminobenzoic acid 0.75 ml (5.08 mmol) and it was stirred at room temperature for 17 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.80 g (yield 78.9 %) were obtained.

(0284)

NMR (CDCl3) delta: 1.39 (3H, t, J = 7 Hz), 4.35 (2H, J = 7 Hz), 7.14-7.20 (1H, m), 7.35-7.43 (4H, m), 7.50 (1H, dd, J = 8 Hz, 1 Hz), 7.57-7.67 (4H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.90 (1H, d, J = 8 Hz), 11.48 (1H, s).

(0285)

Reference Example 28

2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid.

(0286)

(0287)

1M-sodium hydroxide solution 20 ml were added to ethanol (20 ml) solution of 2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid ethyl ester 1.79 g (3.99 mmol) produced in Reference Example 27, and it was heated with stirring for two hours, and next ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.52 g (yield 90.5 %) were obtained.

(0288)

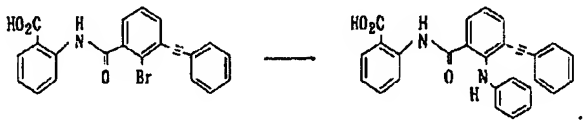
NMR (DMSO-d6) delta: 7.23-7.29 (1H, m), 7.44-7.52 (3H, m), 7.56-7.72 (5H, m), 7.81 (1H, dd, J = 8 Hz, 1 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.57 (1H, d, J = 8 Hz).

(0289)

Example 39

2-(2-phenylamino-3-phenyl-ethynyl benzamide) benzoic acid.

(0290)



(0291)

Potassium carbonate 0.11 g (0.80 mmol) and 5 wt.% activated copper was added to aniline (2 ml) solution of 2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.71 mmol) produced in Reference Example 28, and it was heated with stirring at 180 degrees for two hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate,

and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.17 g (yield 56.3 %) were obtained.

(0292)

NMR (CDCl3) delta: 6.82 (1H, s), 6.93-6.98 (1H, m), 7.03-7.10 (3H, m), 7.14-7.28 (8H, m), 7.38 (1H, dd, J = 7.1 Hz), 7.43-7.48 (1H, m), 7.79 (1H, dd, J = 8 Hz, 1 Hz), 7.97 (1H, dd, J = 8 Hz, 1 Hz), 8.26 (1H, d, J = 8 Hz), 10.82 (1H

IR (ν, cm-1, KBr): 688,1636, 1604, 1524, 1240,762,740,698.

EI-MS (m/z, %): 32 (m +,67), 414 (5), 296 (100), 267 (29).

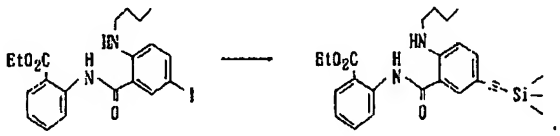
mp: 57-258 degrees.

(0293)

Reference Example 29

2-(2-butylamino-5-trimethylsilylethynyl benzamide) benzoic acid ethyl ester.

(0294)



(0295)

Trimethylsilylacetylene 2.3 ml (16.59 mmol), dichlorobis triphenylphosphine palladium 90 mg (0.13 mmol) and copper iodide 50 mg (0.26 mmol) were added to diethylamine (80 ml) solution of 2-(2-butylamino 5-iodobenzamide) benzoic acid ethyl ester 6.45 g (13.82 mmol) and were stirred at room temperature for one hour 30 minutes, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 4.5 g (yield 74.6 %) were obtained.

(0296)

NMR (CDCl3) delta: 0.25 (9H, s), 0.96 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.42-1.50 (2H, m), 1.62-1.71 (2H, m), 3.14-3.22 (2H, m), 4.42 (2H, q, J = 7 Hz), 6.63 (1H, d, J = 9 Hz), 7.11 (1H, ddd, J

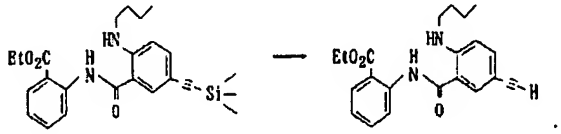
= 8 Hz, 7 Hz, 1 Hz), 7.42 (1H, dd, J = 9 Hz, 2 Hz), 7.57 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.86 (1H, d, J = 2 Hz), 7.95-8.01 (1H, m), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.65 (1H, dd, J = 8 Hz, 1 Hz), 11.69 (1H, s).

(0297)

Reference Example 30

2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester.

(0298)



(0299)

1M-tetrabutyl ammonium fluoride tetrahydrofuran solution 11 ml (11.0 mmol) were added to tetrahydrofuran (60 ml) solution of 2-(2-butylamino-5-trimethylsilylethynyl benzamide) benzoic acid ethyl ester 4.36 g (9.99 mmol) produced in Reference Example 29, and it was stirred under ice cooling for one hour. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 3.06 g (yield 84.0 %) were obtained.

(0300)

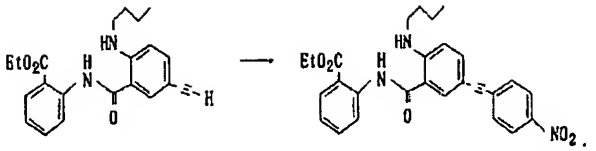
NMR (CDCl3) delta: 0.96 (3H, t, J = 7 Hz), 1.40-1.52 (5H, m), 1.64-1.72 (2H, m), 2.99 (1H, s), 3.16-3.23 (1H, m), 4.43 (2H, q, J = 7 Hz), 6.65 (1H, d, J = 9 Hz), 7.11 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.44 (1H, dd, J = 9 Hz, 2 Hz), 7.57 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.88 (1H, d, J = 2 Hz), 7.98-8.06 (1H, m), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.77 (1H, s).

(0301)

Reference Example 31

2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid ethyl ester.

(0302)



(0303)

4-iodo nitrobenzene 270 ml (1.09 mmol), dichlorobis triphenylphosphine palladium 14 mg (0.01 mmol) and copper iodide 8 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 300 mg (0.82 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for one hour, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 383 mg (yield 95.8 %) were obtained.

(0304)

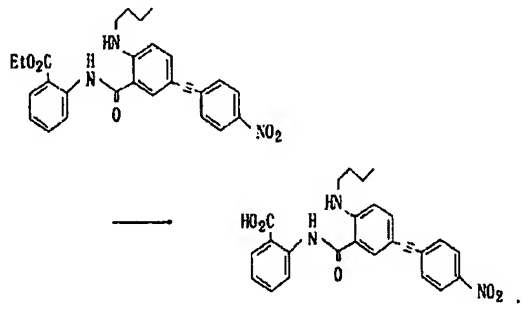
NMR (CDCl3) delta: 0.98 (3H, t, J = 7 Hz), 1.40-1.55 (5H, m), 1.63-1.74 (2H, m), 3.17-3.26 (2H, m), 4.43 (2H, q, J = 7 Hz), 6.71 (1H, d, J = 9 Hz), 7.11-7.16 (1H, m), 7.51 (1H, dd, J = 9 Hz, 2 Hz), 7.57-7.65 (3H, m), 7.95 (1H, d, J = 2 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.20 (2H, d, J = 9 Hz), 8.68 (1H, d, J = 8 Hz), 11.82 (1H, s).

(0305)

Example 40

2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid.

(0306)



(0307)

1M-sodium hydroxide solution 2 ml were added to dioxane (10 ml) solution of 2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid ethyl ester 250 mg (0.51 mmol) produced in Reference Example 31, and the mixture was stirred at room temperature for 18 hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 210 mg (yield 86.4 %) were obtained.

(0308)

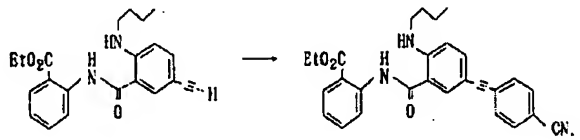
NMR (CDCl3) delta: 0.99 (3H, t, J = 7 Hz), 1.44-1.54 (2H, m), 1.67-1.76 (2H, m), 3.24 (2H, t, J = 7 Hz), 6.72 (1H, d, J = 9 Hz), 6.99-7.05 (1H, m), 7.50 (1H, dd, J = 9 Hz, 2 Hz), 7.58 (2H, d, J = 9 Hz, 2 Hz), 7.63 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.92 (1H, d, J = 2 Hz), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.09 (2H, d, J = 9 Hz), 8.18-8.30 (1H, m), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.63 (1H, s).
IR (v, cm-1, KBr): 3452, 2964, 2196, 1658, 1588, 1520, 1340, 1258, 1218,856,748.
EI-MS (m/z, %): 457 (m +,14), 439 (89), 410 (25), 396 (66), 368 (18), 350 (13), 321 (100).
mp: 179-180 degrees.

(0309)

Reference Example 32

2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid ethyl ester.

(0310)



(0311)

4-iodo benzonitrile 250 mg (1.09 mmol), dichlorobis triphenylphosphine palladium 14 mg (0.01 mmol) and copper iodide 8 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 300 mg (0.82 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for two hours, and next

diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 210 mg (yield 54.7 %) were obtained.

(0312)

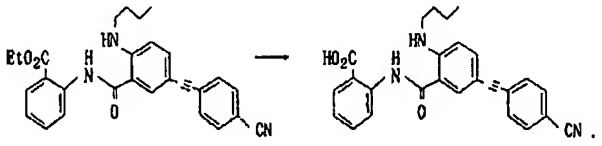
NMR (CDCl3) delta: 0.97 (3H, t, J = 7 Hz), 1.40-1.52 (5H, m), 1.64-1.74 (2H, m), 3.22 (2H, dt, J = 7 Hz, 5 Hz), 4.43 (2H, q, J = 7 Hz), 6.70 (1H, d, J = 9 Hz), 7.11-7.16 (1H, m), 7.45-7.52 (1H, m), 7.55-7.64 (5H, m), 7.93 (1H, d, J = 2 Hz), 8.08-8.16 (2H, m), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.80 (1H, s).

(0313)

Example 41

2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid.

(0314)



(0315)

1M-sodium hydroxide solution 5 ml were added to dioxane (10 ml) solution of 2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid ethyl ester 210 mg (0.45 mmol) produced in Reference Example 32, and the mixture was stirred at room temperature for 24 hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 120 mg (yield 61.0 %) were obtained.

(0316)

NMR (CDCl3) delta: 0.99 (3H, t, J = 7 Hz), 1.41-1.54 (2H, m), 1.67-1.75 (2H, m), 3.23 (2H, t, J = 7 Hz), 6.71 (1H, d, J = 9 Hz), 7.03-7.09 (1H, m), 7.49 (1H, dd, J = 9 Hz, 2 Hz), 7.52-7.56 (4H, m),

7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.91 (1H, d, J = 2 Hz), 8.05 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.67 (1H, s).

IR (ν, cm-1, KBr): 2964, 2248, 2204, 1654, 1598, 1530, 1298, 1218, 834, 756.

EI-MS (m/z, %): 437 (m +,1), 419 (100), 390 (24), 376 (85), 348 (24).

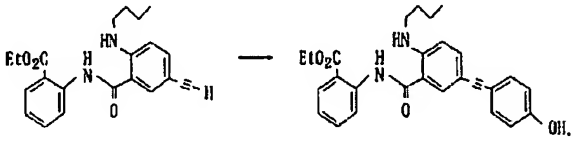
mp: 197-198 degrees.

(0317)

Reference Example 33

2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid ethyl ester.

(0318)



(0319)

4-t-butyldimethylsilyloxy iodo benzene 410 ml (1.23 mmol), dichlorobis triphenylphosphine palladium 14 mg (0.01 mmol) and copper iodide 8 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 300 mg (0.82 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for 19 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, tetrahydrofuran (10 ml) was added, and 1M-tetrabutyl ammonium fluoride tetrahydrofuran solution 1.3 ml (1.3 mmol) were added, and it was stirred with ice cooling for one hour. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 184 mg (yield 49.0 %) were obtained.

(0320)

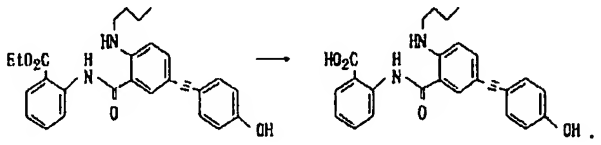
NMR (CDCl3) delta: 0.97 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.44-1.54 (2H, m), 1.62-1.72 (2H, m), 3.17-3.26 (2H, m), 4.43 (2H, q, J = 7 Hz), 4.90 (1H, s), 6.68 (1H, d, J = 9 Hz), 6.80 (2H, d, J = 9 Hz), 7.09-7.14 (1H, m), 7.41 (2H, d, J = 9 Hz), 7.47 (1H, dd, J = 9 Hz, 2 Hz), 7.55-7.61 (1H, m), 7.88 (1H, d, J = 2 Hz), 7.94-8.00 (1H, m), 8.09 (1H, dd, 8 Hz, 1 Hz), 8.67 (1H, d, J = 8 Hz), 11.74 (1H, s).

(0321)

Example 42

2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid.

(0322)



(0323)

1M-sodium hydroxide solution 10 ml were added to dioxane (20 ml) solution of 2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid ethyl ester 180 mg (0.39 mmol) produced in Reference Example 33, and the mixture was stirred at room temperature for four hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 116 mg (yield 56.7 %) were obtained.

(0324)

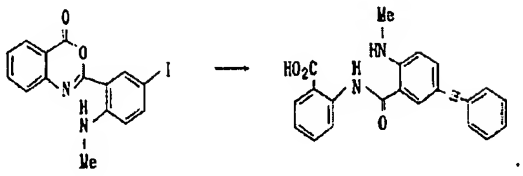
NMR (DMSO-d6) delta: 0.94 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.56-1.64 (2H, m), 3.18-3.24 (2H, m), 6.76-6.84 (3H, m), 7.18-7.24 (1H, m), 7.32 (2H, d, J = 9 Hz), 7.48 (1H, dd, J = 9 Hz, 2 Hz), 7.61-7.67 (1H, m), 7.84 (1H, d, J = 2 Hz), 8.00-8.07 (2H, m), 8.53 (1H, dd, J = 8 Hz, 1 Hz), 11.96 (1H, s)
IR (ν, cm-1, KBr): 3336, 2964, 1648, 1606, 1526, 1256, 1210,836, 762.
EI-MS (m/z, %): 428 (m +,4), 410 (100), 381 (6), 367 (17), 321 (20).
mp: 197-198 degrees.

(0325)

Example 43

2-(2-methylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0326)



(0327)

Ethynylbenzene 0.2 ml (1.72 mmol), dichlorobis triphenylphosphine palladium 10 mg (0.01 mmol) and copper iodide 6 mg (0.02 mmol) were added to triethylamine (10 ml) and tetrahydrofuran (15 ml) solution of 2-(2-methylamino-5-iodophenyl)-4-oxo-4H-3,1-benzoxazine 500 mg (1.32 mmol), and under a nitrogen atmosphere, it was stirred at room temperature for four hours, and next triethylamine was eliminated by distillation under reduced pressure. Saturated aqueous sodium bicarbonate solution was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in 20 ml dioxane, and 1M-sodium hydroxide solution 10 ml were added, and the mixture was stirred at room temperature for 18 hours, and next dioxane was eliminated by distillation under reduced pressure. 2M-hydrochloric acid was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 340 mg (yield 69.7 %) were obtained.

(0328)

NMR (DMSO-d6) delta: 2.28 (3H, d, J = 5 Hz), 6.79 (1H, d, J = 9 Hz), 7.18-7.24 (1H, m), 7.38-7.46 (3H, m), 7.48-7.53 (2H, m), 7.56 (1H, dd, J = 9 Hz, 2 Hz), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.88 (1H, d, J = 2 Hz), 7.90-7.96 (1H, m), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.54 (1H, dd, J = 8 Hz, 1 Hz), 11.93 (1H, s).

IR (ν, cm-1, KBr): 3404, 2208, 1664, 1528, 1214,756.

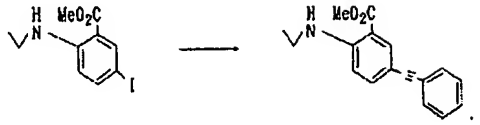
EI-MS (m/z, %): 370 (m +,100), 352 (48), 323 (7), 233 (62) mp. 205-206 degrees.

(0329)

Reference Example 34

2-ethylamino-5-phenyl-ethynyl methyl benzoate ester.

(0330)



(0331)

Ethynylbenzene 1.0 ml (9.43 mmol), dichlorobis triphenylphosphine palladium 55 mg (0.08 mmol) and copper iodide 30 mg (0.16 mmol) were added to diethylamine (25 ml) solution of 2-ethylamino-5-iodobenzoic acid methyl 2.24 g (7.86 mmol), and the mixture was stirred at room temperature for 24 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 1.26 g (yield 57.4 %) were obtained.

(0332)

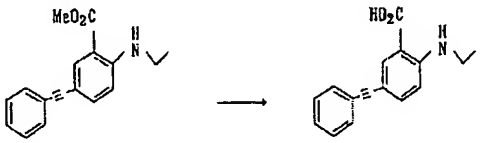
NMR (CDCl3) delta: 1.33 (3H, t, J = 7 Hz), 3.26 (2H, ddd, J = 14 Hz, 7 Hz, 5 Hz), 6.65 (1H, d, J = 9 Hz), 7.28-7.35 (3H, m), 7.46-7.52 (3H, m), 7.80-7.86 (1H, m), 8.11 (1H, d, J = 2 Hz).

(0333)

Reference Example 35

2-ethylamino-5-phenyl-ethynyl benzoic acid.

(0334)



(0335)

1M-sodium hydroxide solution 10 ml were added to ethanol (20 ml) solution of 2-ethylamino-5-phenyl-ethynyl methyl benzoate 1.26 g (4.51 mmol) produced in Reference Example 34 and were heated under reflux for three hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. 2M-hydrochloric acid solution was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.96 g (yield 80.2 %) were obtained.

(0336)

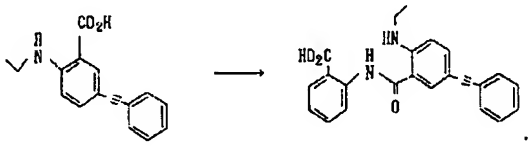
NMR (DMSO-d6) delta: 1.22 (3H, t, J = 7 Hz), 3.25 (2H, q, J = 7 Hz), 6.77 (1H, d, J = 9 Hz), 7.36-7.43 (3H, m), 7.48-7.55 (3H, m), 7.94 (1H, d, J = 2 Hz).

(0337)

Example 44

2-(2-ethylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0338)



(0339)

Thionyl chloride 0.13 ml (1.81 mmol) were added under a nitrogen atmosphere to anhydrous benzene solution (15 ml) of 2-ethylamino-5-phenyl-ethynyl benzoic acid 400 mg (1.51 mmol) produced in Reference Example 35 and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. To anhydrous toluene (20 ml) solution of the residue, 2-aminobenzoic acid 0.25 g (1.51 mmol) and potassium carbonate 0.21 g (1.81 mmol) were added and under a nitrogen atmosphere, were heated under reflux for seven hours and thereafter, were cooled to room temperature. Water was added to the reaction solution, and thereafter, the organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by

distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.25 g (yield 60.4 %) were obtained.

(0340)

NMR (DMSO-d6) delta: 1.23 (3H, t, J = 7 Hz), 3.20-3.26 (2H, m), 6.83 (1H, d, J = 9 Hz), 7.18-7.24 (1H, m), 7.37-7.46 (3H, m), 7.48-7.56 (3H, m), 7.62-7.68 (1H, m), 7.89 (1H, d, J = 2 Hz), 7.93-8.00 (1H, m), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.52 (1H, dd, J = 8 Hz, 1 Hz), 11.95 (1H, s) IR (v, cm-1, KBr): 3328, 2972, 2212, 1654, 1534, 1252, 1222,756.

EI-MS (m/z, %): 384 (m +,100), 366 (92), 337 (22), 323 (27), 247 (44), 232 (25).

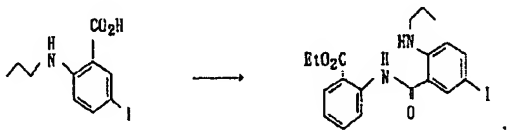
mp: 202-204 degrees.

(0341)

Reference Example 36

2-(2-propylamino-5-iodo benzamide) benzoic acid ethyl ester.

(0342)



(0343)

Thionyl chloride 0.34 ml (4.72 mmol) were added under a nitrogen atmosphere to anhydrous benzene solution (20 ml) of 2-propylamino-5-iodobenzoic acid 1.2 g (3.93 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. To anhydrous toluene (30 ml) solution of the residue, 2-ethyl aminobenzoic acid 0.7 ml (4.72 mmol) and potassium carbonate 0.65 g (4.72 mmol) were added and under a nitrogen atmosphere, it was heated under reflux for seven hours and thereafter, was cooled to room temperature. Water was added to the reaction solution, and thereafter, the organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 1.0 g (yield 56.3 %) were obtained.

(0344)

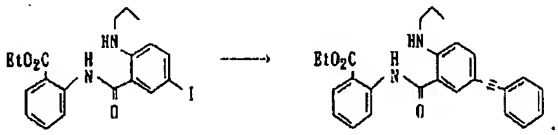
NMR (CDCl3) delta: 1.02 (3H, t, J = 7 Hz), 1.45 (3H, t, J = 7 Hz), 1.70 (2H, hex, J = 7 Hz), 3.12 (2H, dt, J = 7.5 Hz), 4.44 (2H, q, J = 7 Hz), 6.50 (1H, d, J = 9 Hz), 7.11 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.52-7.60 (2H, m), 7.75-7.84 (1H, m), 7.96 (1H, d, J = 2 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.67 (1H, dd, J = 8 Hz, 1 Hz), 11.74 (1H, s).

(0345)

Reference Example 37

2-(2-propylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0346)



(0347)

Ethynylbenzene 0.16 ml (1.78 mmol), dichlorobis triphenylphosphine palladium 10 mg (0.01 mmol) and copper iodide 6 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-propylamino-5-iodo benzamide) benzoic acid ethyl ester 500 mg (1.10 mmol) produced in Reference Example 36, and the mixture was stirred at room temperature for 20 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.38 g (yield 81.8 %) were obtained.

(0348)

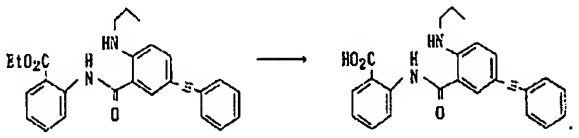
NMR (CDCl3) delta: 1.04 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.72 (2H, Hex, J = 7 Hz), 3.18 (2H, dt, J = 7.5 Hz), 4.43 (2H, q, J = 7 Hz), 6.69 (1H, d, J = 9 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.28-7.36 (3H, m), 7.47-7.53 (3H, m), 7.58 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.92 (1H, d, J = 2 Hz), 8.00-8.06 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.77 (1H, s).

(0349)

Example 45

2-(2-propylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0350)



(0351)

1M-sodium hydroxide solution 10 ml were added to dioxane (20 ml) solution of 2-(2-propylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 380 mg (0.89 mmol) produced in Reference Example 37, and the mixture was heated under reflux for four hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 250 mg (yield 70.5 %) were obtained.

(0352)

NMR (DMSO-d6) delta: 0.98 (3H, t, J = 7 Hz), 1.63 (2H, hex, J = 7 Hz), 3.14-3.24 (2H, m), 6.83 (1H, d, J = 9 Hz), 7.18-7.25 (1H, m), 7.38-7.45 (3H, m), 7.48-7.56 (3H, m), 7.60-7.68 (1H, m), 7.90 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.07-8.12 (1H, m), 8.52 (1H, d, J = 8 Hz), 11.95 (1H, s).

IR (ν, cm-1, KBr): 3324, 2212, 1658, 1532, 1254, 1220,756.

EI-MS (m/z, %): 398 (m +,100), 380 (35), 351 (27), 323 (7), 232 (58).

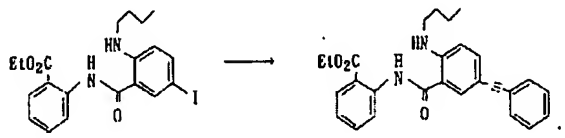
mp: 193-194 degrees.

(0353)

Reference Example 38

2-(2-butylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0354)



(0355)

Ethynylbenzene 0.16 ml (1.78 mmol), dichlorobis triphenylphosphine palladium 10 mg (0.01 mmol) and copper iodide 6 mg (0.02 mmol) were added to diethylamine (10 ml) solution of ethyl 2-(2-butylamino-5-iodobenzamide) benzoic acid ethyl ester 500 mg (1.07 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for 19 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.38 g (yield 80.6 %) were obtained.

(0356)

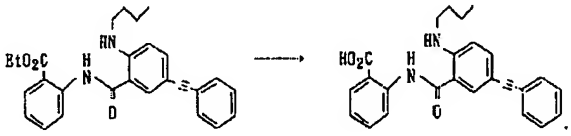
NMR (CDCl3) delta: 0.97 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.43-1.52 (2H, m), 1.64-1.74 (2H, m), 3.18-3.26 (2H, m), 4.42 (2H, q, J = 7 Hz), 6.69 (1H, d, J = 9 Hz), 7.09-7.14 (1H, m), 7.26-7.36 (3H, m), 7.47-7.54 (3H, m), 7.54-7.62 (1H, m), 7.91 (1H, d, J = 2 Hz), 7.97-8.04 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.76 (1H, s).

(0357)

Example 46

2-(2-butylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0358)



(0359)

1M-sodium hydroxide solution 10 ml were added to dioxane (20 ml) solution of 2-(2-butylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 380 mg (0.86 mmol) produced in Reference Example 38, and the mixture was heated under reflux for 6 hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 294 mg (yield 82.7 %) were obtained.

(0360)

NMR (CDCl3) delta: 0.98 (3H, t, J = 7 Hz), 1.48 (2H, hex, J = 7 Hz), 1.6-1.74 (2H, m), 3.22 (2H, t, J = 7 Hz), 6.71 (1H, d, J = 9 Hz), 6.93-6.98 (1H, m), 7.23-7.30 (2H, m), 7.48-7.54 (3H, m), 7.60 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.91 (1H, d, J = 2 Hz), 8.00 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.68 (1H, s).

IR (ν, cm-1, KBr): 3368, 3320, 2964, 2216, 1652, 1528, 1252, 1218, 756.

EI-MS (m/z, %): 412 (m +,100), 394 (26), 351 (22), 323 (7), 232 (71).

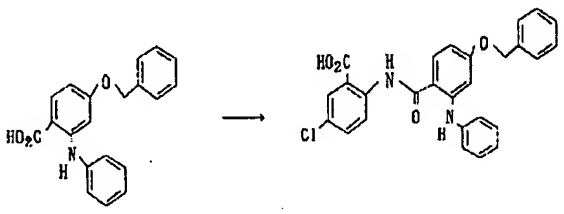
mp: 188-189 degrees.

(0361)

Example 47

5-chloro-2-(4-benzyloxy-2-phenylamino benzamide) benzoic acid.

(0362)



(0363)

To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 0.50 g (1.56 mmol), thionyl chloride 0.28 g (2.35 mmol) was added under a nitrogen atmosphere, and it was stirred under ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to 2-amino-5-chlorobenzoic acid 0.40 g (2.35 mmol) and methylene chloride (15 ml) solution of triethylamine 0.65 ml (2.35 mmol) and was stirred at room temperature for 17 hours. Water was added to the reaction solution, and extraction was carried out with methylene chloride. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 390 mg (yield 53.0 %) were obtained.

(0364)

NMR (DMSO-d6) delta: 5.14 (2H, s), 6.62 (1H, dd, J = 9 Hz, 2 Hz), 6.80 (1H, d, J = 2 Hz), 7.02 (1H, t, J = 7 Hz), 7.12 (2H, d, J = 7 Hz), 7.25-7.41 (7H, m), 7.69 (1H, dd, J = 9 Hz, 2 Hz), 7.74 (1H, d, J = 9 Hz), 7.96 (1H, d, J = 2 Hz), 8.59 (1H, d, J = 9 Hz), 9.70 (1H, s), 11.87 (1H, s).

IR (ν, cm-1, KBr): 1652, 1582, 1434, 1256,752.

EI-MS (m/z, %): 472 (m +,6), 386 (15), 329 (13), 301 (7), 251 (10), 119 (10), 91 (100).

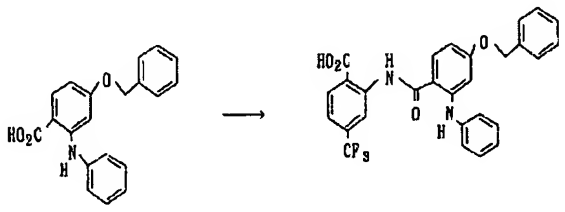
mp: 229-230 degrees.

(0365)

Example 48

2-(4-benzyloxy-2-phenylamino benzamide)-4-trifluoromethyl benzoic acid.

(0366)



(0367)

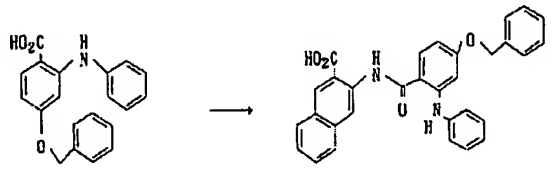
To methylene chloride (15 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol), thionyl chloride 186 mg (1.56 mmol) was added, and it was stirred under ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to methylene chloride (15 ml) suspending solution of 2-amino-4-trifluoromethyl benzoic acid 480 mg (2.35 mmol) and potassium carbonate 539 mg (3.9 mmol), and it was stirred for one hour, and thereafter, triethylamine 1 ml (2.35 mmol) was added, and it was stirred at room temperature furthermore for 15 hours. 1M-hydrochloric acid was added to the reaction solution, and the organic layer was extracted with methylene chloride. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 370 mg (yield 46.5 %) were obtained.

(0368)

NMR (DMSO-d6) delta: 5.13 (2H, s), 6.64 (1H, dd, J = 9 Hz, 2 Hz), 6.79 (1H, d, J = 2 Hz), 7.03 (1H, t, J = 7 Hz), 7.14 (2H, dd, J = 8 Hz, 1 Hz), 7.27-7.44 (7H, m), 7.53 (1H, dd, J = 8 Hz, 1 Hz), 7.76 (1H, d, J = 9 Hz), 8.21 (1H, d, J = 8 Hz), 8.95 (1H, d, J = 1 Hz), 9.60 (1H, s), 12.00 (1H, s).
IR (ν, cm-1, KBr): 1645, 1597, 1573, 1521, 1233,749.
EI-MS (m/z, %): 506 (m +,53), 488 (9), 446 (4), 329 (5), 302 (17), 301 (39), 300 (16), 272 (9), 211 (7), 91 (100).
mp: 207-208 degrees.

(0369)
Example 49
3-(4-benzyloxy-2-phenylamino benzamide)-2-naphtalenecarboxylic acid.

(0370)



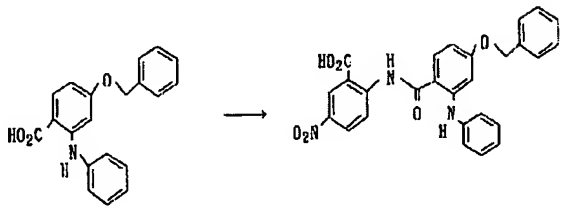
(0371)
To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol), thionyl chloride 186 mg (1.56 mmol) were added under ice cooling and were stirred for two hours. This solution was dropwise-added to 3-amino-2 naphtalenecarboxylic acid 438 mg (2.34 mmol) and methylene chloride (15 ml) solution of triethylamine 1.09 ml (7.83 mmol) and was stirred at room temperature for three days. The reaction solution was acidified with 1M-hydrochloric acid, and extraction was carried out with acetic acid ethyl ester. It was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethanol, and title compound 438 mg (yield 57.0 %) were obtained.

(0372)
NMR (DMSO-d6) delta: 5.15 (2H, s), 6.64 (1H, dd, J = 9 Hz, 2 Hz), 6.83 (1H, d, J = 2 Hz), 7.03 (1H, t, J = 7 Hz), 7.15 (2H, d, J = 8 Hz), 7.29-7.42 (7H, m), 7.50 (1H, t, J = 7 Hz), 7.63 (1H, t, J = 8 Hz), 7.81 (1H, d, J = 9 Hz), 7.94 (1H, d, J = 8 Hz), 8.05 (1H, d, J = 8 Hz), 8.74 (1H, s), 9.04 (1H, s), 9.87 (1H, s), 12.06 (1H, s).
IR (ν, cm-1, KBr): 3352, 1694, 1642, 1546, 1254,740.

EI-MS (m/z, %): 488 (m +,5), 446 (9), 386 (6), 330 (5), 329 (10), 328 (5), 251(11), 129 (9), 121 (9), 119 (10), 97 (8), 91 (72).
mp: 268 degrees.

(0373)
Example 50
2-(4-benzyloxy-2-phenylamino benzamide)-5-nitrobenzoic acid.

(0374)



(0375)
To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 580 mg (1.82 mmol), thionyl chloride 324 mg (2.72 mmol) was added under ice cooling, and it was stirred with ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to 2-amino-5-nitrobenzoic acid 365 mg (2.00 mmol) and methylene chloride (10 ml) solution of triethylamine 0.76 ml (5.46 mmol) and was stirred at room temperature for 20 hours. Water was added to the reaction solution and was extracted with methylene chloride. It was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 440 mg (yield 50.0 %) were obtained.

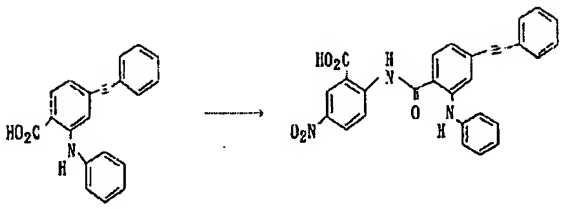
(0376)
NMR (DMSO-d6) delta: 5.04 (2H, s), 6.51 (1H, dd, J = 9 Hz, 2 Hz), 6.82 (1H, d, J = 2 Hz), 7.10 (1H, dd, J = 7 Hz, 7 Hz), 7.17 (2H, dd, J = 8 Hz, 1 Hz), 7.30-7.41 (7H, m), 8.45 (1H, dd, J = 9 Hz, 2 Hz), 7.72 (1H, d, J = 9 Hz), 9.00-9.10 (2H, s), 9.91 (1H, s), 11.99 (1H, s).
IR (v, cm-1, KBr): 1694, 1658, 1550, 1228,756,744.
FAB-MS (m/z, %): 484 (M-H, 3), 302 (100).
mp: 202-203 degrees.

(0377)

Example 51

5-nitro-2-(2-phenylamino 4-phenyl-ethynyl benzamide) benzoic acid.

(0378)



(0379)

To methylene chloride (10 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 200 mg (0.64 mmol), thionyl chloride 114 mg (0.96 mmol) was added under ice cooling, and it was stirred with ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to 2-amino-5-nitrobenzoic acid 174 mg (0.96 mmol) and methylene chloride (10 ml) solution of triethylamine 0.26 ml (1.91 mmol) and was stirred at room temperature for 20 hours. Water was added to the reaction solution and was extracted with methylene chloride. It was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 92 mg (yield 30.0 %) were obtained.

(0380)

NMR (DMSO-d6) delta: .07 (1H, t, J = 7 Hz), 7 .13 (1H, dd, J = 8 Hz, 1 Hz), 7.23 (2H, d, J = 7 Hz), 7.34-7.59 (8H, m), 7.83 (1H, d, J = 8 Hz), 8.49 (1H, dd, J = 9 Hz, 3 Hz), 8.76 (1H, d, J = 3 Hz), 8.84 (1H, d, J = 9 Hz), 9.27 (1H, s), 12.48 (1H, s).

IR (ν, cm-1, KBr): 2212, 1704, 1636, 1596, 1514, 1220,762.

FAB-MS (m/z, %): 476 (M-H, 100).

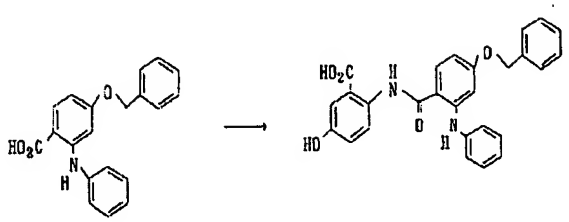
mp: 248-250 degrees.

(0381)

Example 52

2-(4-benzyloxy-2-phenylamino benzamide)-5-hydroxybenzoic acid.

(0382)



(0383)

To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol), it was added thionyl chloride 0.15 ml (2.00 mmol), and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. To toluene (20 ml) solution of the residue, 2-amino-5-hydroxybenzoic acid 240 mg (1.56 mmol) and potassium carbonate 330 mg (2.39 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography and recrystallisation from acetonitrile, and title compound 243 mg (yield 34.0 %) were obtained.

(0384)

NMR (DMSO-d6) delta: 5.13 (2H, s), 6.59 (1H, dd, J = 9 Hz, 2 Hz), 6.80 (1H, d, J = 2 Hz), 6.98-7.04 (2H, m), 7.11 (2H, d, J = 8 Hz), 7.25-7.43 (8H, m), 7.72 (1H, d, J = 9 Hz), 8.31 (1H, d, J = 9 Hz), 9.61 (1H, s), 9.83 (1H, s), 11.62 (1H, m).

IR (v, cm-1, KBr): 3364, 1668, 1644, 1614, 1588, 1546, 1524, 1498, 1472, 1288, 1252, 1226, 1192,762,740.

FAB-MS (m/z, %): 453 (M-H, 100)

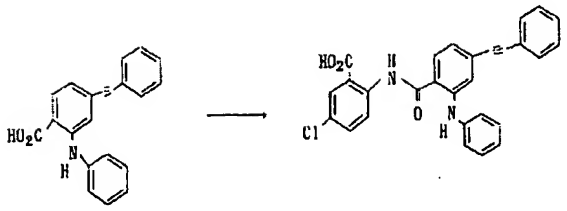
mp. 212-214 degrees.

(0385)

Example 53

5-chloro-2-(2-phenylamino 4-phenyl-ethynyl benzamide) benzoic acid.

(0386)



(0387)

To methylene chloride (15 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 250 mg (0.80 mmol), thionyl chloride 0.07 ml (0.96 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (20 ml) solution of the residue, 2-amino-5-chlorobenzoic acid 171 mg (1.0 mmol) and potassium carbonate 276 mg (2.0 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 300 mg (yield 80.0 %).

(0388)

NMR (DMSO-d6) delta: 7.06 (1H, t, J = 7 Hz), 7.11 (1H, dd, J = 8 Hz, 1 Hz), 7.22 (2H, d, J = 7 Hz), 7.33-7.39 (3H, m), 7.41-7.46 (3H, m), 7.54-7.59 (2H, m), 7.71 (1H, dd, J = 9 Hz, 2 Hz), 7.80 (1H, d, J = 8 Hz), 7.97 (1H, d, J = 2 Hz), 8.57 (1H, d, J = 9 Hz), 9.30 (1H, s), 12.00 (1H, s).

IR (ν, cm-1, KBr): 3384, 3208, 1704, 1636, 1608, 1580, 1550, 1518, 1496, 1286, 1222, 1222, 1188,750,692.

EI-MS (m/z, %): 466 (m +,4), 296 (6), 295 (10), 91 (100).

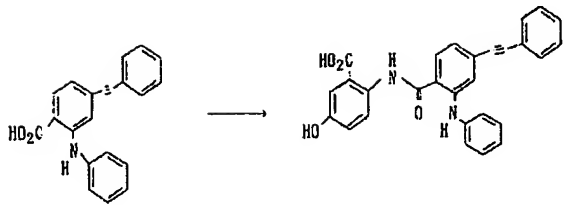
mp: 256-257 degrees.

(0389)

Example 54

5-hydroxy-2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0390)



(0391)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.15 ml (2.00 mmol) was added, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 2-amino-5-hydroxybenzoic acid 294 mg (1.92 mmol) and potassium carbonate 266 mg (1.92 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and title compound 500 mg (yield 70.0 %) were obtained.

(0392)

NMR (DMSO-d6) delta: 7.03-7.13 (3H, m), 7.23 (2H, dd, J = 8 Hz, 1 Hz), 7.34-7.45 (7H, m), 7.54-7.59 (2H, m), 7.79 (1H, d, J = 8 Hz), 8.29 (1H, d, J = 9 Hz), 9.41 (1H, s), 9.68 (1H, s), 11.58 (1H, s), 13.58 (1H, m).

IR (v, cm-1, KBr): 3344, 3048, 1680, 1648, 1588, 1534, 1498, 1416, 1290, 1254, 1220,754.

FAB-MS (m/z, %): 447 (M-H, 100).

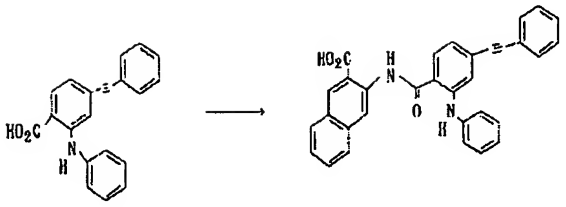
mp: 233-234 degrees.

(0393)

Example 55

3-(2-phenylamino-4-phenyl-ethynyl benzamide)-2-naphtalenecarboxylic acid.

(0394)



(0395)

To methylene chloride (25 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.4 ml (1.92 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 3-amino-2-naphtalenecarboxylic acid 450 mg (1.92 mmol) and potassium carbonate 265 mg (1.92 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography and methanol washing, and title compound 286 mg (yield 37.0 %) were obtained.

(0396)

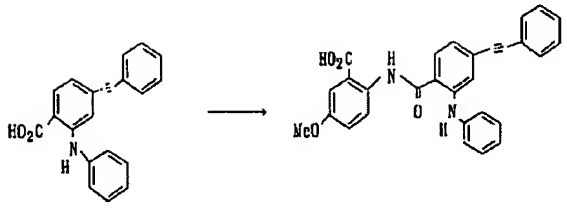
NMR (DMSO-d6) delta: 7.07 (1H, t, J = 7 Hz), 7.14 (1H, dd, J = 8 Hz, 1 Hz), 7.25-7.29 (2H, m), 7.35-7.46 (6H, m), 7.50-7.60 (4H, m), 7.62-7.68 (1H, m), 7.87 (1H, d, J = 8 Hz), 7.94 (1H, d, J = 8 Hz), 8.07 (1H, d, J = 8 Hz), 8.75 (1H, s), 9.04 (1H, s), 9.47 (1H, s), 12.11 (1H, s), 13.6-14.4 (1H, m).
IR (ν, cm-1, KBr): 3360, 3132, 3056, 1698, 1638, 1548, 1276, 1262, 1194,754,692.
EI-MS (m/z, %): 482 (m +,17), 464 (6), 446 (15), 295 (32), 278 (13), 91 (100).
mp: 264 degrees (dec.).

(0397)

Example 56

5-methoxy-2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0398)



(0399)

To methylene chloride (25 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.14 ml (1.92 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 2-amino-5-methoxybenzoic acid 379 mg (2.27 mmol) and potassium carbonate 265 mg (1.92 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and title compound 436 mg (yield 59.0 %) were obtained.

(0400)

NMR (DMSO-d6) delta: 7.06 (1H, t, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1 Hz), 7.21-7.28 (3H, m), 7.33-7.39 (3H, m), 7.41-7.46 (3H, m), 7.50 (1H, d, J = 3 Hz), 7.54-7.59 (2H, m), 7.80 (1H, d, J = 8 Hz), 8.40 (1H, d, J = 9 Hz), 9.39 (1H, s), 11.66 (1H, s).

IR (v, cm-1, KBr): 3348, 1700, 1684, 1636, 1610, 1598, 1536, 1496, 1416, 1324, 1286, 1222, 1176, 1042,830,750.

EI-MS (m/z, %): 462 (m +,84), 444 (26), 426 (7), 296 (90), 295 (100), 267 (14), 167 (34).

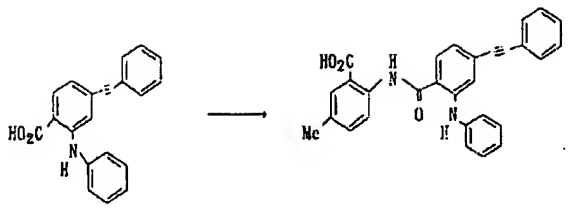
mp: 234-235 degrees.

(0401)

Example 57

5-methyl-2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0402)



(0403)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 300 mg (0.96 mmol), thionyl chloride 0.08 ml (1.1 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 2-amino-5-methylbenzoic acid 174 mg (1.15 mmol) and potassium carbonate 159 mg (1.15 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 375 mg (yield 88.0 %).

(0404)

NMR (DMSO-d6) delta: 2.33 (3H, s), 7.06 (1H, t, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1 Hz), 7.24 (2H, dd, J = 8 Hz, 1 Hz), 7.33-7.45 (6H, m), 7.47 (1H, dd, J = 8 Hz, 1 Hz), 7.54-7.60 (2H, m) 7.80 (1H, d, J = 8 Hz), 7.85 (1H, d, J = 2 Hz), 8.46 (1H, d, J = 8 Hz), 9.39 (1H, s), 11.95 (1H, s) 13.5-13.9 (1H, m).

IR (ν, cm-1, KBr): 3228, 2212, 1698, 1640, 1596, 1582, 1536, 1496, 1416, 1322, 1290, 1256, 1224, 1176, 1060,750.

EI-MS (m/z, %): 446 (m +,7), 428 (2), 295 (10), 267 (2).

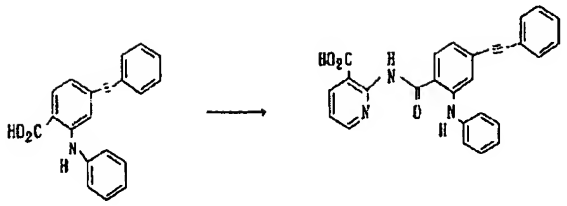
mp: 248-250 degrees.

(0405)

Example 58

2-(2-phenylamino-4-phenyl-ethynyl benzamide) nicotinic acid.

(0406)



(0407)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 300 mg (0.96 mmol), thionyl chloride 0.08 ml (1.1 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-amino nicotinic acid 145 mg (1.05 mmol) and triethylamine 1 ml were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 124 mg (yield 30.0 %).

(0408)

NMR (DMSO-d6) delta: 7.04-7.10 (2H, m), 7.21-7.25 (2H, m), 7.32-7.46 (7H, m) 7.55-7.60 (2H, m), 7.88 (1H, d, J = 8 Hz), 8.26 (1H, dd, J = 8 Hz, 1 Hz), 8.59 (1H, dd, J = 5.2 Hz), 9.20-9.40 (1H, m), 11.40-11.60 (1H, m).

IR (ν, cm-1, KBr): 3444, 3256,3100-2900, 2212, 1756, 1664, 1640, 1594, 1554, 1518, 1496, 1444, 1412, 1316, 1272, 1258, 1244, 1210,770,752.

FAB-MS (m/z, %): 434 (M + H, 17), 296 (100).

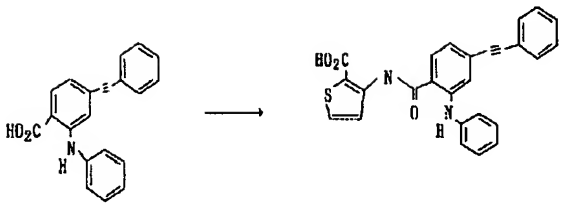
mp: 236-237 degrees.

(0409)

Example 59

3-(2-phenylamino-4-phenyl-ethynyl benzamide) thiophencarboxylic acid.

(0410)



(0411)

To methylene chloride (15 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 250 mg (0.8 mmol), thionyl chloride 0.08 ml (1.0 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 3-amino-2-thiophencarboxylic acid methyl ester 151 mg (0.96 mmol) and potassium carbonate 133 mg (0.96 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography. Obtained ester was dissolved in ethanol (25 ml) and 1M-sodium hydroxide solution 1.4 ml were added and were heated under reflux for four hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. The residue was acidified with hydrochloric acid, and next precipitate was filtered, and it was recrystallised from acetonitrile, and it was obtained title compound 236 mg (yield 78.0 %).

(0412)

NMR (DMSO-d6) delta: 7.05 (1H, t, J = 7 Hz), 7.15 (1H, dd, J = 8 Hz, 1 Hz), 7.20 (2H, dd, J = 8 Hz, 1 Hz), 7.32-7.46 (6H, m), 7.55-7.60 (2H, m), 7.79 (1H, d, J = 8 Hz), 7.90 (1H, d, J = 5 Hz), 8.08 (1H, d, J = 5 Hz), 9.20 (1H, s), 11.36 (1H, s), 13.5-13.7 (1H, m).

IR (v, cm-1, KBr): 3392, 3260, 3044, 2636, 2212, 1640, 1608, 1554, 1498, 1446, 1408, 1368, 1258, 1242, 1214,756.

EI-MS (m/z, %): 420 (m +,41), 296 (100), 278 (75), 256 (38), 205 (55), 178 (46), 147 (46), 133 (54), 129 (62), 121 (58), 119 (48), 115 (50), 108 (70), 105 (69).

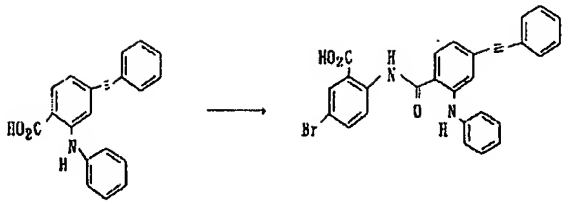
mp: 218-220 degrees.

(0413)

Example 60

5-bromo-2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0414)



(0415)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.15 ml (2.00 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-amino-5-bromobenzoic acid 415 mg (1.92 mmol) and potassium carbonate 266 mg (1.92 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 455 mg (yield 55.6 %).

(0416)

NMR (DMSO-d6) delta: 7.06 (1H, t, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1, Hz), 7.23 (2H, dd, J = 8 Hz, 1 Hz), 7.33-7.48 (6H, m), 7.54-7.60 (2H, m), 7.80 (1H, d, J = 8 Hz), 7.84 (1H, dd, J = 9 Hz, 2 Hz) 8.09 (1H, d, J = 2 Hz), 8.52 (1H, d, J = 9 Hz), 9.30 (1H, s), 11.96 (1H, s).

IR (ν, cm-1, KBr): 3220, 2220, 1700, 1688, 1636, 1606, 1596, 1576, 1516, 1496, 1418, 1370, 1322, 1284, 1250, 1220, 1180,824,790,764,750.

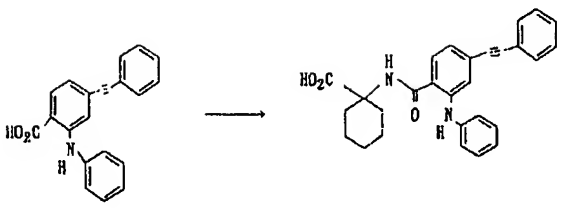
EI-MS (m/z, %): 512 (m +,10), 494 (4), 295 (30), 267 (7), 239 (1), 190 (1), 163 (1), 91 (2) mp. 261-263 degrees.

(0417)

Example 61

1-(2-phenylamino-4-phenyl-ethynyl benzamide) cyclohexanecarboxylic acid.

(0418)



(0419)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 500 mg (1.6 mmol), thionyl chloride 0.15 ml (2 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 1,1-aminocyclohexanecarboxylic acid benzyl 448 mg (1.92 mmol) and potassium carbonate 266 mg (1.92 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with acetonitrile. Obtained crystals were dissolved in ethanol (10 ml) and 1M-sodium hydroxide solution 2 ml were added and were heated under reflux for five hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. The residue was acidified with hydrochloric acid, and next precipitate was filtered, and it was recrystallised from ether, and it was obtained title compound 434 mg (yield 62.0 %).

(0420)

NMR (DMSO-d6) delta: 1.22-1.35 (1H, m), 1.43-1.62 (5H, m), 1.68-1.82 (2H, m), 2.03-2.18 (2H, m), 7.01-7.07 (2H, m), 7.18 (2H, dd, J = 8 Hz, 1 Hz), 7.31-7.45 (6H, m), 7.54-7.59 (2H, m), 7.73 (1H, d, J = 8 Hz, Hz), 8.52 (1H, s), 9.27 (1H, s), 12.27 (1H, s).

IR (v, cm-1, KBr): 3432, 3396, 3236, 3040, 2932, 2860, 2624, 2208, 1718, 1634, 1590, 1558, 1516, 1496, 1418, 1270, 1172,868,782,758.

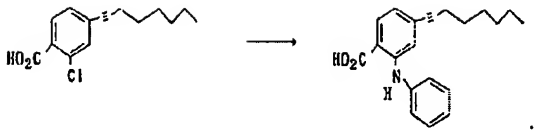
EI-MS (m/z, %): 438 (m +,49), 420 (8), 394 (3), 349 (14), 295 (100), 267 (14), 239 (3), 163 (3), 98 (6), 81 (3) mp. 194-195 degrees.

(0421)

Reference Example 39

4-(octan-1-yl)-2-phenylamino benzoic acid.

(0422)



(0423)

To aniline (20 ml) solution of 2-chloro-4-(octan-1-yl) benzoic acid 1.95 g (7.36 mmol) were added potassium carbonate 1.22 g (8.83 mmol) and 5 wt.% activated copper and it was heated under reflux for three hours, and aniline was eliminated by distillation under reduced pressure. The residue was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with methylene chloride, and it was recrystallised from methanol, and title compound 2.12 g (yield 90.0 %) were obtained.

(0424)

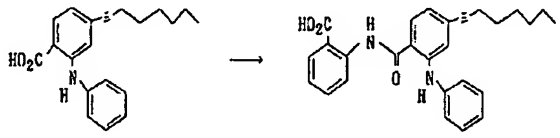
NMR (CDCl3) delta: 0.89 (3H, t, J = 7 Hz), 1.23-1.43 (6H, m), 1.57 (2H, q, J = 7 Hz) 2.37 (2H, t, J = 7 Hz), 6.75 (1H, dd, J = 8 Hz, 1 Hz), 7.15 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.21 (1H, d, J = 1 Hz), 7.24-7.29 (2H, m), 7.35-7.42 (2H, m), 7.93 (1H, d, J = 8 Hz), 9.28 (1H, s).

(0425)

Example 62

2-(4-(octan-1-yl)-2-phenylamino phenylamino benzamide) benzoic acid.

(0426)



(0427)

To methylene chloride (20 ml) solution of 4-(octan-1-yl)-2-phenylamino benzoic acid 520 mg (1.62 mmol) produced in Reference Example 39 was added thionyl chloride 0.12 ml (1.62 mmol), and it was stirred at room temperature for three hours, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue were added 2-

aminobenzoic acid 267 mg (1.94 mmol) and potassium carbonate 268 mg (1.94 mmol) and triethylamine 0.27 ml (1.94 mmol), and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 450 mg (yield 63 %) were obtained.

(0428)

NMR (CDCl3) delta: 0.88 (3H, t, J = 7 Hz), 1.20-1.44 (10H, m), 1.50-1.60 (2H, m) 2.38 (2H, t, J = 7 Hz), 6.87 (1H, dd, J = 7.1 Hz), 7.07 (1H, t, J = 7 Hz), 7.14-7.20 (1H, m), 7.23-7.30 (2H, m), 7.32-7.39 (3H, m), 7.64-7.70 (2H, m), 8.15-8.21 (1H, m), 8.83 (1H, dd, J = 8 Hz, 1 Hz), 9.61 (1H, s), 11.69 (1H, s).

IR (v, cm-1, KBr): 3300, 3044, 2228, 1682, 1652, 1606, 1580, 1562, 1542, 1516, 1498, 1470, 1452, 1420, 1320, 1294, 1258, 1224, 1160, 1068, 1028,870,752.

EI-MS (m/z, %): 440 (m +,100), 422 (24), 303 (59), 260 (20), 246 (20), 233 (31), 204 (23).

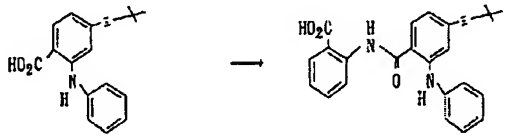
mp: 165-167 degrees.

(0429)

Example 63

2-(4-(3,3-dimethyl butenyl)-2-phenylamino benzamide) benzoic acid.

(0430)



(0431)

To methylene chloride (20 ml) solution of 4-(3,3-dimethyl butenyl)-2-phenylamino benzoic acid 587 mg (2.00 mmol) was added thionyl chloride 0.2 ml (2.67 mmol), and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-aminobenzoic acid 302 mg (2.20 mmol), potassium carbonate 304 mg (2.20 mmol) and triethylamine 0.30 ml (2.20 mmol) were added, and the mixture was stirred at room temperature for 18 hours. The reaction solution was

acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 654 mg (yield 79.0 %) were obtained.

(0432)

NMR (CDCl3) delta: 1.30 (9H, s), 6.87 (1H, dd, J = 8 Hz, 1 Hz), 7.04-7.10 (1H, m), 7.14-7.20 (1H, m), 7.23-7.29 (2H, m), 7.32-7.39 (3H, m), 7.63-7.70 (2H, m), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, dd, J = 8 Hz, 1 Hz), 9.60 (1H, s), 11.67 (1H, s).

IR (v, cm-1, KBr): 3288, 2972, 2224, 1656, 1608, 1582, 1560, 1532, 1498, 1420, 1294, 1256, 1224, 1162,900,764,75 2.

EI-MS (m/z, %): 412 (m +,44), 394 (6), 295 (2), 275 (76), 260 (38), 246 (5).

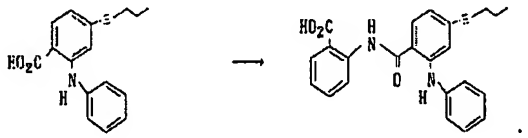
mp: 225-227 degrees.

(0433)

Example 64

2-(2-phenylamino-4-(pentan-1-yl) benzamide) benzoic acid.

(0434)



(0435)

To methylene chloride (25 ml) solution of 2-phenylamino-4-(pentan-1-yl) benzoic acid 510 mg (1.83 mmol) was added thionyl chloride 0.14 ml (1.83 mmol), and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-aminobenzoic acid 302 mg (2.20 mmol), potassium carbonate 304 mg (2.20 mmol) and triethylamine 0.30 ml (2.20 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by

distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 530 mg (yield 73.0 %) were obtained.

(0436)

NMR (CDCl3) delta: 1.03 (3H, t, J = 7 Hz) 1.50-1.65 (2H, m), 2.37 (2H, t, J = 7.1 Hz), 6.88 (1H, dd, J = 1.5 Hz, 8.3 Hz), 7.07 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.14-7.21 (1H, m), 7.23-7.30 (2H, m), 7.32-7.40 (3H, m), 7.63-7.71 (2H, m), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, dd, J = 8 Hz, 1 Hz), 9.60 (1H, s), 11.67 (1H, s).

IR (ν, cm-1, KBr): 3256, 3020, 2872, 2224, 1656, 1606, 1582, 1562, 1534, 1498, 1470, 1452, 1420, 1318, 1258, 1222, 1162,892,758,.

EI-MS (m/z, %): 398 (m +,45 %), 380 (6), 261 (54), 233 (17), 204(11), 190 (2), 146 (2), 119 (3).

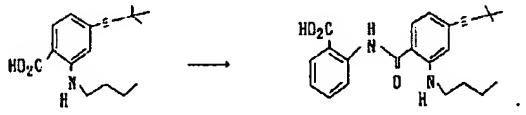
mp: 199-200 degrees.

(0437)

Example 65

2-(2-butylamino-4-(3,3-dimethyl butenyl) benzamide) benzoic acid.

(0438)



(0439)

To methylene chloride (15 ml) solution of 2-butylamino-4-(3,3-dimethyl butenyl) benzoic acid 547 mg (2.00 mmol) was added thionyl chloride 0.2 ml (2.67 mmol), and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-aminobenzoic acid 302 mg (2.20 mmol), potassium carbonate 304 mg (2.20 mmol) and triethylamine 0.30 ml (2.20 mmol) were added, and the mixture was stirred at room temperature for 16 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 659 mg (yield 84.0 %) were obtained.

(0440)

NMR (CDCl3) delta: 0.97 (3H, t, J = 7 Hz), 1.34 (9H, s), 1.42-1.53 (2H, m), 1.65-1.73 (2H, m), 3.16-3.20 (2H, m), 6.69 (1H, dd, J = 8 Hz, 2 Hz), 6.74 (1H, d, J = 2 Hz), 7.14 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.59 (1H, d, J = 8 Hz), 7.63 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz).

IR (ν, cm-1, KBr): 3332, 3072, 2964, 2228, 1650, 1608, 1536, 1220, 766,754.

FAB-MS (m/z, %): 391(M-H).

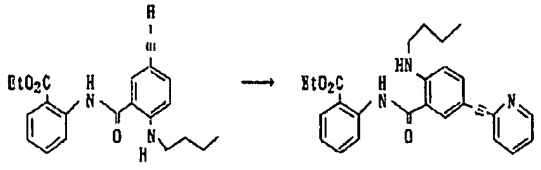
mp: 225-227 degrees.

(0441)

Reference Example 40

2-(2-butylamino-5-(2-pyridyl ethynyl) benzamide) benzoic acid ethyl ester.

(0442)



(0443)

2-iodopyridine 0.30 ml (2.89 mmol), dichlorobis triphenylphosphine palladium 16 mg (0.01 mmol) and copper iodide 10 mg (0.03 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 526 mg (1.44 mmol), and the mixture was stirred at room temperature for two hours. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, saturated aqueous potassium hydrogen sulphate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 375 mg (yield 77.5 %) were obtained.

(0444)

NMR (CDCl3) delta: 0.97 (3H, t, J = 7 Hz), 1.42 (3H, t, J = 7 Hz), 1.40-1.50 (2H, m), 1.64-1.71 (2H, m), 3.18-3.24 (2H, m), 4.43 (2H, q, J = 7 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.19 (1H, ddd, J = 8 Hz, 5,1 Hz), 7.50 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.55-7.61 (2H, m), 7.66 (1H, ddd, J = 8 Hz, 8

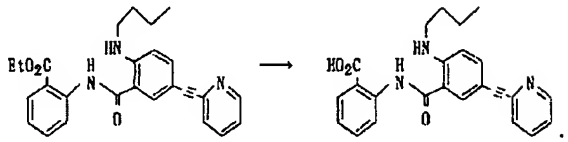
Hz, 2 Hz), 7.97 (1H, d, J = 2 Hz), 8.06 (1H, t, J = 5 Hz), 8.10 (1H, dd, J = 8 Hz, 2 Hz), 8.58-8.61 (1H, m), 8.66 (1H, dd, J = 8 Hz, 1 Hz), 11.77 (1H, s).

(0445)

Example 66

2-(2-butylamino-5-(2-pyridyl ethynyl) benzamide) benzoic acid.

(0446)



(0447)

1M-sodium hydroxide solution 1 ml was added to ethanol (20 ml) solution of 2-(2-butylamino-5-(2-pyridyl ethynyl) benzamide) benzoic acid ethyl ester 375 mg (0.85 mmol) produced in Reference Example 40 and it was heated under reflux for two hours and thereafter, it was cooled to room temperature. The reaction solution was neutralised with saturated potassium hydrogensulfate, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 194 mg (yield 55.0 %) were obtained.

(0448)

NMR (DMSO-d6) delta: 0.94 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.57-1.65 (2H, m), 3.21-3.26 (2H, m), 6.86 (1H, d, J = 9 Hz), 7.19-7.24 (1H, m), 7.37 (1H, ddd, J = 8 Hz, 5,1 Hz), 7.56-7.60 (2H, m), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 2 Hz), 7.83 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.96 (1H, d, J = 2 Hz), 8.04 (1H, dd, J = 8 Hz, 2 Hz), 8.18 (1H, t, J = 5 Hz), 8.54 (1H, dd, J = 8 Hz, 1 Hz), 8.57-8.60 (1H, m), 12.03 (1H, s).

IR (ν, cm-1, KBr): 2204, 1652, 1590, 1528, 1220, 770, 756.

FAB-MS (m/z, %): 412 (M-H, 100).

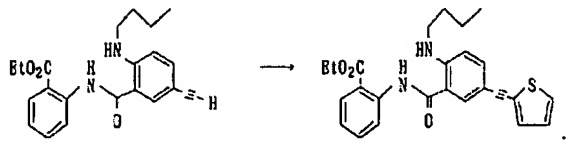
mp: 179-180 degrees.

(0449)

Reference Example 41

2-(2-butylamino-5-(2-thiophenyl ethynyl) benzamide) benzoic acid ethyl ester.

(0450)



(0451)

2-iodo thiophene 0.30 ml (2.89 mmol), dichlorobis triphenylphosphine palladium 16 mg (0.01 mmol) and copper iodide 10 mg (0.03 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 500 mg (1.37 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for two hours. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, saturated aqueous potassium hydrogen sulphate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 233 mg (yield 38.0 %) were obtained.

(0452)

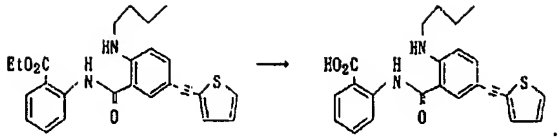
NMR (CDCl3) delta: 0.97 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.41-1.52 (2H, m), 1.64-1.73 (2H, m), 3.18-3.22 (2H, m), 4.43 (2H, q, J = 7 Hz), 6.69 (1H, d, J = 9 Hz), 7.00 (1H, dd, J = 5.4 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.23-7.26 (2H, m), 7.47 (1H, dd, J = 8 Hz, 1 Hz), 7.58 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.89 (1H, J = 2 Hz), 8.03 (1H, t, J = 5 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.67 (1H, dd, J = 8 Hz, 1 Hz).

(0453)

Example 67

2-(2-butylamino-5-(2-thiophenyl ethynyl) benzamide) benzoic acid.

(0454)



(0455)

1M-sodium hydroxide solution 1 ml was added to ethanol (20 ml) solution of 2-(2-butylamino-5-(2-thiophenyl ethynyl) benzamide) benzoic acid ethyl ester 230 mg (0.52 mmol) produced in Reference Example 41 and was heated under reflux for three hours and thereafter, it was cooled to room temperature. The reaction solution was neutralised with saturated potassium hydrogensulfate, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 185 mg (yield 85.0 %) were obtained.

(0456)

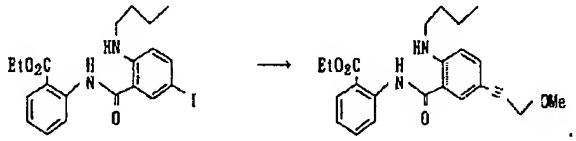
NMR (DMSO-d6) delta: 0.94 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.56-1.64 (2H, m), 3.19-3.25 (2H, m), 6.83 (1H, d, J = 9 Hz), 7.11 (1H, dd, J = 5 Hz, 4 Hz), 7.18-7.24 (1H, m), 7.35 (1H, dd, J = 4 Hz, 1 Hz) 7.52 (1H, dd, J = 9 Hz, 2 Hz), 7.60-7.67 (2H, m), 7.88 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.11 (1H, dd, J = 8 Hz, 1 Hz), 8.51 (1H, dd, J = 8 Hz, 1 Hz), 11.97 (1H, s).
IR (ν, cm-1, KBr): 3320, 2964, 2208, 1652, 1602, 1530, 1254,756.
FAB-MS (m/z, %): 417 (M-H, 16), 189 (100)
mp. 79-180 degrees.

(0457)

Reference Example 42

2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) benzoic acid ethyl ester.

(0458)



(0459)

3-methoxy-1-propine 0.25 ml (3.00 mmol), dichlorobis triphenylphosphine palladium 53 mg (0.08 mmol) and copper iodide 14 mg (0.08 mmol) were added to mixed solution of 10 ml of tetrahydrofuran and 20 ml of diethylamine containing 2-(2-butylamino-5-iodo benzamide) benzoic acid ethyl ester 700 mg (1.50 mmol) produced in Reference Example 30 and were stirred at room temperature for two hours. Water was added, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated potassium hydrogensulfate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 375 mg (yield 61.2 %) were obtained.

(0460)

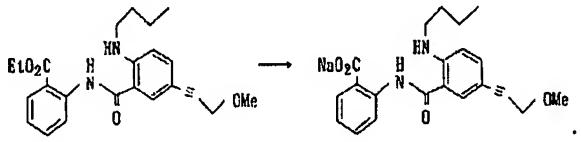
NMR (CDCl3) delta: 0.96 (3H, t, J = 7 Hz), 1.40-1.51 (5H, m), 1.62-1.71 (2H, m), 3.16-3.22 (2H, m), 3.47 (3H, s), 4.20 (2H, q, J = 7 Hz), 4.34 (2H, s), 7.11 (1H, ddd, J = 8.7,1 Hz), 7.41 (1H, dd, J = 8 Hz, 2 Hz), 7.57 (1H, ddd, J = 8.7,1 Hz), 7.84 (1H, d, J = 2 Hz), 8.00 (1H, t, J = 5 Hz), 8.09 (1H, dd, J = 8.1 Hz), 8.68 (1H, dd, J = 8.1 Hz), 11.75 (1H, s).

(0461)

Example 68

2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) sodium benzoate salt.

(0462)



(0463)

1M-sodium hydroxide solution 2 ml were added to mixed solution of 20 ml of tetrahydrofuran and 20 ml of ethanol containing 2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) benzoic acid ethyl ester 370 mg (0.91 mmol) produced in Reference Example 42, and the mixture was stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol-ether-hexane, and title compound 300 mg (yield 85.9 %) were obtained.

(0464)

NMR (DMSO-d6) delta: 0.93 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.55-1.64 (2H, m), 3.15-3.21 (2H, m), 4.31 (2H, s), 6.73 (1H, d, J = 9 Hz), 6.96-7.01 (1H, m), 7.28-7.33 (1H, m), 7.39 (1H, dd, J = 9 Hz, 2 Hz), 7.90 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.37 (1H, t, J = 5 Hz), 8.54 (1H, d, J = 8 Hz).

IR (ν, cm-1, KBr): 3300, 2956, 2928, 2212, 1652, 1590, 1522, 1296, 760.

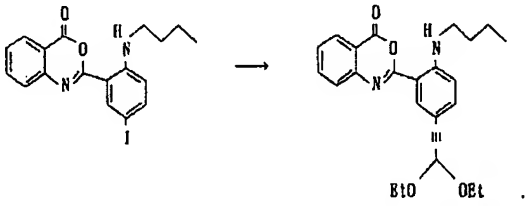
FAB-MS (m/z, %): 424 (m + Na, 100) mp. 179-180 degrees.

(0465)

Reference Example 43

2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) phenyl)-4-oxo-4H-3,1-benzoxazine

(0466)



(0467)

Propargyl aldehyde diethyl acetal 0.96 ml (1.72 mmol), dichlorobis triphenylphosphine palladium 30 mg (0.03 mmol) and copper iodide 20 mg (0.06 mmol) were added to triethylamine (30 ml) and tetrahydrofuran (15 ml) solution of 2-(2-butylamino-5-iodo phenyl)-4-oxo-4H-3,1-benzoxazine 1.40 g (3.33 mmol), and under a nitrogen atmosphere, it was stirred at room temperature for one hour. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, saturated aqueous potassium hydrogen sulphate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 625 mg (yield 41.4 %) were obtained.

(0468)

NMR (CDCl3) delta: 1.04 (3H, t, J = 7 Hz), 1.29 (6H, t, J = 7 Hz), 1.53-1.63 (2H, m), 1.75-1.84 (2H, m), 3.29-3.34 (2H, m), 3.63-3.72 (2H, m), 3.80-3.89 (2H, m), 5.50 (1H, s), 6.68 (1H, d, J = 9 Hz),

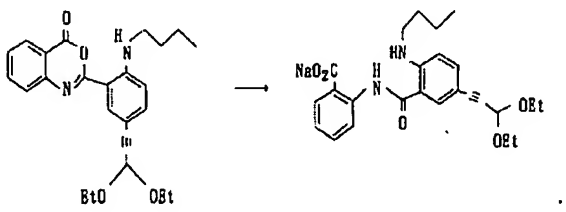
7.43-7.52 (3H, m), 7.80 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.22 (1H, ddd, J = 8 Hz, 1,1 Hz), 8.32 (1H, d, J = 2 Hz), 9.25 (1H, t, J = 5 Hz).

(0469)

Example 69

2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) benzamide) sodium benzoate salt.

(0470)



(0471)

1M-sodium hydroxide solution 5 ml were added to mixed solution of 20 ml of tetrahydrofuran and 20 ml of ethanol containing 2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) phenyl)-4-oxo-4H-3,1-benzoxazine 600 mg (1.43 mmol) produced in Reference Example 43, and the mixture was stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol-ether-hexane, and title compound 580 mg (yield 88.0 %) were obtained.

(0472)

NMR (CDCl3) delta: 0.93 (3H, t, J = 7 Hz), 1.18 (6H, t, J = 7 Hz), 1.38-1.46 (2H, m), 1.55-1.64 (2H, m), 3.16-3.21 (2H, m), 3.53-3.61 (2H, m), 3.65-3.73 (2H, m), 5.50 (1H, s), 6.75 (1H, d, J = 9 Hz), 6.98-7.03 (1H, m), 7.31-7.36 (1H, m), 7.40 (1H, dd, J = 9 Hz, 2 Hz), 7.89 (1H, d, J = 2 Hz), 8.06-8.09 (1H, m), 8.39 (1H, t, J = 5 Hz), 8.55 (1H, dd, J = 8 Hz, 1 Hz).

IR (ν, cm-1, KBr): 2960, 2932, 2220, 1660, 1594, 1520, 1288,754.

FAB-MS (m/z, %): 437 (M-H, 34), 379 (100).

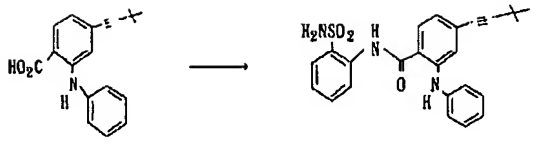
mp: 179-180 degrees.

(0473)

Example 70

4-(3,3-dimethyl butenyl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0474)



(0475)

4-(3,3-dimethyl butenyl)-2-phenylamino benzoic acid 1.0 g (3.40 mmol) and methylene chloride (30 ml) solution of thionyl chloride 0.4 ml were stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (30 ml) solution of the residue was dropwise-added under ice cooling to pyridine (50 ml) solution of 2-aminobenzene sulfonamide 0.65 g (3.75 mmol), and it was stirred at room temperature for 18 hours, and next methylene chloride was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.8 g (yield 52.0 %) were obtained.

(0476)

NMR (CDCl3) delta: 1.29 (9H, s), 4.87 (2H, br-s), 6.85 (1H, dd, J = 8 Hz, 2 Hz), 7.09 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.21-7.29 (3H, m), 7.52-7.59 (2H, m), 7.57 (1H, d, J = 8 Hz), 7.63 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz), 8.41 (1H, dd, J = 8 Hz, 1 Hz), 9.53 (1H, s), 10.03 (1H, s).

IR (ν, cm-1, KBr): 3364, 2972, 2928, 2224, 1642, 1586, 1556, 1516, 1500, 1472, 1442, 1420, 1334, 1290, 1272, 1222, 1154,764.

FAB-MS (m/z, %): 446 (M-H, 100).

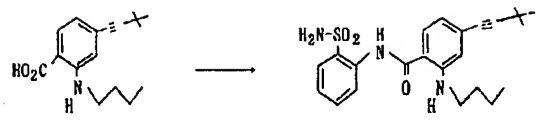
mp: 101-102 degrees.

(0477)

Example 71

2-butylamino-4-(3,3-dimethyl butenyl)-N-(2-sulphamoyl phenyl) benzamide.

(0478)



(0479)

2-butylamino-4-(3,3-dimethyl butenyl) benzoic acid 1.0 g (3.66 mmol) and methylene chloride (30 ml) solution of thionyl chloride 0.4 ml were stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (30 ml) solution of the residue was dropwise-added under ice cooling to pyridine (50 ml) solution of 2-aminobenzene sulfonamide 0.7 g (4.03 mmol), and it was stirred at room temperature for 18 hours, and next methylene chloride was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.9 g (yield 54.0 %) were obtained.

(0480)

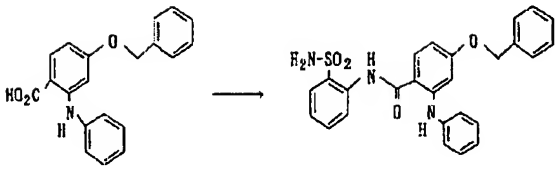
NMR (DMSO-d6) delta: 0.97 (3H, t, J = 7 Hz), 1.34 (9H, s), 1.41-1.51 (2H, m), 1.62-1.72 (2H, m), 3.18 (2H, t, J = 7 Hz), 4.83 (2H, br-s), 6.45 (1H, dd, J = 8.2 Hz), 6.74 (1H, d, J = 2 Hz), 7.23 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.48 (1H, d, J = 8 Hz), 7.61 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.86 (1H, br-s), 7:95 (1H, dd, J = 8 Hz, 2 Hz), 8.34 (1H, dd, J = 8 Hz, 1 Hz), 9.70 (1H, s).
IR (ν, cm-1, KBr): 3368, 3232, 3084, 2968, 2932, 2868, 2224, 1644, 1600, 1584, 1564, 1530, 1472, 1440, 1342, 1292, 1226, 1168, 1156,896,764.
FAB-MS (m/z, %): 426 (M-H, 100).
mp: 130-131 degrees.

(0481)

Example 72

4-benzyloxy-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0482)



(0483)

To methylene chloride (15 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol) was added thionyl chloride 186 mg (1.56 mmol) under ice cooling, and it was stirred at room temperature for two hours. This solution was dropwise-added to 2-aminobenzene sulfonamide 174 mg (0.96 mmol) and methylene chloride (15 ml) solution of triethylamine 1 ml (7.8 mmol) and was stirred at room temperature for four hours. To the reaction solution, water was added, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography and recrystallisation from ethanol, and title compound 210 mg (yield 28.0 %) were obtained.

(0484)

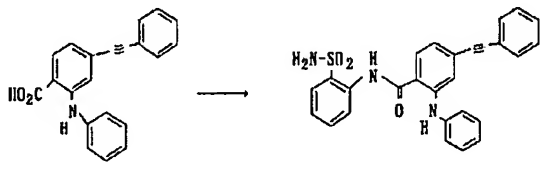
NMR (delta, DMSO-d6): 4.82 (2H, s), 5.04 (2H, s), 6.48 (1H, dd, J = 9 Hz, 2 Hz), 6.85 (1H, d, J = 2 Hz), 7.04-7.10 (1H, m), 7.15 (2H, dd, J = 9 Hz, 2 Hz), 7.22-7.41 (8H, m), 7.60-7.65 (2H, m), 7.98 (1H, dd, J = 8 Hz, 1 Hz), 8.38 (1H, dd, J = 8 Hz, 1 Hz), 9.74 (1H, s), 9.87 (1H, s).
IR (v, cm-1, KBr): 1646, 1580, 1522, 1286,756.
EI-MS (m/z, %): 473 (31), 446 (10), 302 (18), 301 (30), 300(11), 91 (100).
mp: 171-172 degrees.

(0485)

Example 73

4-phenyl-ethynyl-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0486)



(0487)

2-phenylamino-4-phenyl-ethynyl benzoic acid 1 g (3.40 mmol) and methylene chloride (30 ml) solution of thionyl chloride 0.4 ml were stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (30 ml) solution of the residue was dropwise-added under ice cooling to pyridine (50 ml) solution of 2-aminobenzene sulfonamide 0.65 g (3.75 mmol), and it was stirred at room temperature for 18 hours, and next methylene chloride was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.8 g (yield 52.0 %) were obtained.

(0488)

NMR (CDCl3) delta: 1.29 (9H, s), 4.87 (2H, br-s), 6.85 (1H, ddd, J = 8 Hz, 2 Hz, 1 Hz), 7.09 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.21-7.29 (3H, m), 7.52-7.59 (2H, m), 7.57 (1H, d, J = 8 Hz), 7.63 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz), 8.41 (1H, dd, J = 8 Hz, 1 Hz), 9.53 (1H, s), 10.03 (1H, s).

IR (v, cm-1, KBr): 3380, 3320, 3244, 3056, 2212, 1644, 1594, 1582, 1558, 1530, 1500, 1468, 1442, 1424, 1334, 1294, 1226, 1154, 756.

EI-MS (m/z, %): 467 (m +,59), 295 (100), 267 (16).

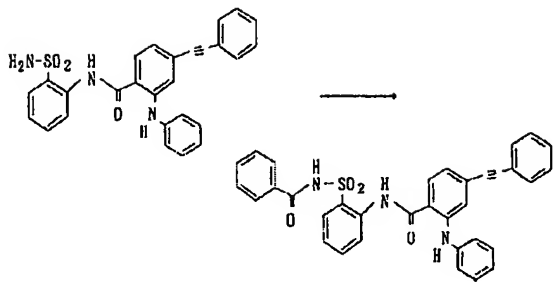
mp: 195-196 degrees.

(0489)

Example 74

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) benzamide.

(0490)



(0491)

To mixed solution of 10 ml of water and 10 ml dioxane, benzoyl chloride 90 mg (0.64 mmol) were dropwise-added, and potassium carbonate 118 mg (0.86 mmol) were stirred at room temperature 4-phenyl-ethynyl-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 200 mg (0.43 mmol) produced in Example 73 for 16 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with methanol, and title compound 168 mg (yield 69.0 %) were obtained.

(0492)

NMR (CDCl3) delta: 7.00 (1H, dd, J = 8 Hz, 1 Hz), 7.07-7.12 (1H, m), 7.27-7.77 (16H, m), 7.92 (1H, d, J = 8 Hz), 8.07 (1H, dd, J = 8 Hz, 1 Hz), 8.62 (1H, dd, J = 8 Hz, 1 Hz), 8.70 (1H, s), 9.60 (1H, s), 10.49 (1H, s).

IR (v, cm-1, KBr): 3384, 3326, 1704, 1660, 1596, 1582, 1562, 1520, 1286, 752.

FAB-MS (m/z, %): 570 (M-H, 100)

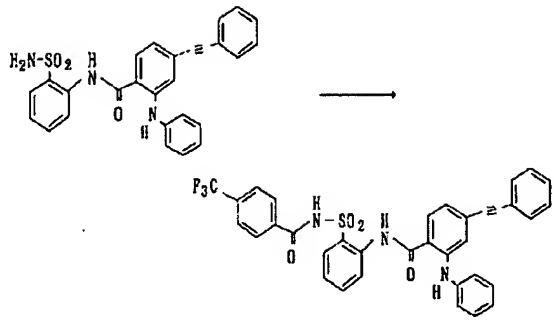
mp. 241-243 degrees.

(0493)

Example 75

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl)-4-trifluoromethyl benzamide.

(0494)



(0495)

To mixed solution of 10 ml water and 10 ml dioxane containing potassium carbonate 118 mg (0.856 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 200 mg (0.43 mmol) produced in Example 73, was added under a stream of nitrogen 4-trifluoromethyl benzoyl chloride 179 mg (0.856 mmol) and the mixture was stirred at room temperature for 16 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with methanol, and the target substance was obtained 168 mg (yield 61.0 %).

(0496)

NMR (CDCl3) delta: 7.04-7.10 (2H, m), 7.21-7.25 (2H, m), 7.32-7.46 (7H, m), 7.55-7.60 (2H, m), 7.88 (1H, d, J = 8 Hz), 8.26 (1H, dd, J = 7 Hz, 2 Hz), 8.59 (1H, dd, J = 5 Hz, 2 Hz), 9.2-9.4 (1H, m), 11.4-11.6 (1H, m).

IR (v, cm-1, KBr): 3320, 3244, 2216, 1706, 1662, 1642, 1594, 1580, 1558, 1528, 1498, 1472, 1442, 1422, 1326, 1288, 1256, 1226, 1156, 1130, 1070,756.

EI-MS (m/z, %): 639 (m +,16), 467 (20), 446 (10), 422 (17), 295 (88), 278 (42).

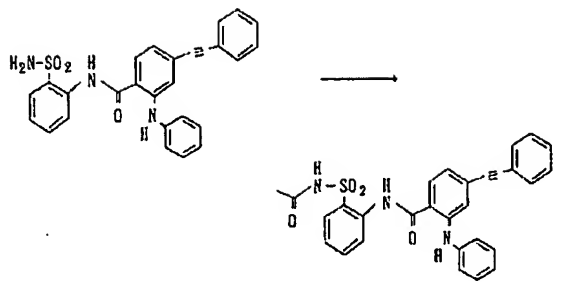
mp: 178-180 degrees.

(0497)

Example 76

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) acetamide.

(0498)



(0499)

Acetic anhydride 0.12 ml (1.28 mmol) were added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 315 mg (2.57 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 400 mg (0.86 mmol) produced in Example 73, and the mixture was stirred at room temperature for two hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 358 mg (yield 82.2 %) were obtained.

(0500)

NMR (CDCl3) delta: 2.08 (3H, s), 6.99 (1H, dd, J = 8 Hz, 1 Hz), 7.07-7.12 (1H, m), 7.26-7.40 (8H, m), 7.46-7.54 (3H, m), 7.66-7.71 (1H, m), 7.82 (1H, d, J = 8 Hz), 8.01 (1H, dd, J = 8 Hz, 1 Hz), 8.06-8.16 (1H, m), 8.58 (1H, dd, J = 8 Hz, 1 Hz), 9.57 (1H, s), 10.30 (1H, s).

IR (ν, cm-1, KBr): 3450-2950, 2864, 2212, 1714, 1660, 1582, 1556, 1530, 1498, 1472, 1442, 1420, 1342, 1318, 1286, 1256, 1224, 1156, 1128,854,756.

EI-MS (m/z, %): 509 (m +,22), 295 (49), 267 (7), 91 (2), 61 (3).

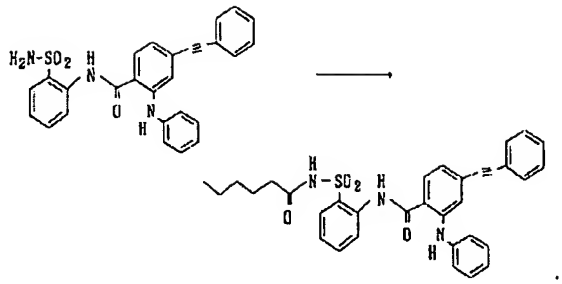
mp: 108 degrees.

(0501)

Example 77

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) hexane amide.

(0502)



(0503)

4-dimethylaminopyridine 260 mg (2.14 mmol) and hexanoyl chloride 0.16 ml (1.17 mmol) were added to tetrahydrofuran (10 ml) solution of 4-phenyl-ethynyl-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 500 mg (1.04 mmol) produced in Example 73, and the mixture was stirred at room temperature for one hour. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 200 mg (yield 33.3 %) were obtained.

(0504)

NMR (CDCl3) delta: 0.84 (3H, t, J = 7 Hz), 1.16-1.32 (4H, m), 1.50-1.62 (2H, m), 2.23 (2H, t, J = 7 Hz), 6.99 (1H, dd, J = 8 Hz, 1 Hz), 7.06-7.12 (1H, m), 7.24-7.30 (3H, m), 7.32-7.40 (5H, m), 7.46-7.54 (3H, m), 7.65-7.71 (1H, m), 7.83 (1H, d, J = 8 Hz), 8.01 (1H, dd, J = 8 Hz, 1 Hz), 8.10 (1H, br-s), 8.57 (1H, dd, J = 8 Hz, 1 Hz), 9.57 (1H, s), 10.31 (1H, s).

IR (v, cm-1, KBr): 2956, 1714, 1660, 1582, 1442, 1286,756,692.

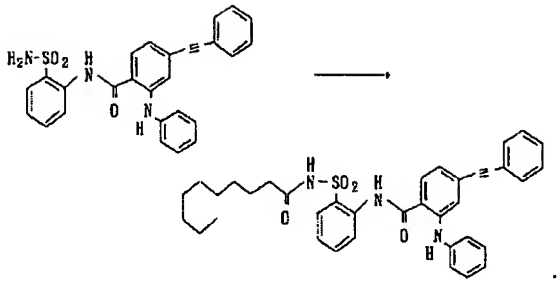
EI-MS (m/z, %): 565 (m +,41), 467 (4), 295 (100), 267 (13), 205 (29).

(0505)

Example 78

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) decane amide.

(0506)



(0507)

Under a stream of nitrogen, decanoyl chloride 153 mg (0.806 mmol) was added to mixed solution of 10 ml water and 10 ml dioxane containing potassium carbonate 148 mg (1.07 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 250 mg (0.54 mmol) produced in Example 73, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride) (and title compound 238 mg (yield 71.5 %) were obtained.

(0508)

NMR (CDCl3) delta: 0.86 (3H, t, J = 7 Hz), 1.12-1.32 (11H, m), 1.50-1.62 (3H, m), 2.23 (2H, t, J = 7 Hz), 6.99 (1H, dd, J = 8 Hz, 1 Hz), 7.09 (1H, t, J = 7 Hz), 7.24-7.42 (8H, m), 7.47-7.68 (1H, t, J = 7 Hz), 7.83 (1H, d, J = 8 Hz), 8.00 (1H, dd, J = 8 Hz, 1 Hz), 8.08 (1H, s), 8.57 (1H, d, J = 8 Hz), 9.57 (1H, s), 10.32 (1H, s).

IR (ν, cm-1, KBr): 3252, 2928, 2856, 2216, 1714, 1668, 1594, 1578, 1564, 1524, 1500, 1470, 1440, 1418, 1342, 1314, 1286, 1226, 1156, 870, 754, 724, 690, 582.

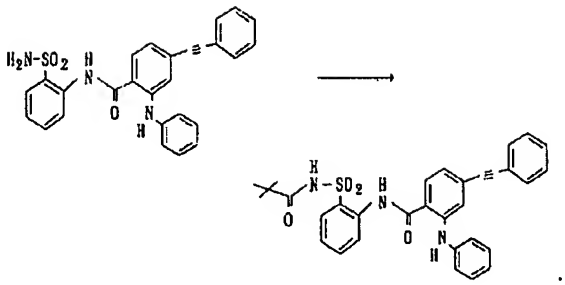
EI-MS (m/z, %): 621 (m +,50 %), 467 (12), 446 (13), 295 (100), 278 (9), 267 (13).

(0509)

Example 79

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) pivalamide.

(0510)



(0511)

Under a stream of nitrogen, pivaloyl chloride 0.07 ml (0.57 mmol) was added to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 118 mg (0.96 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 226 mg (0.48 mmol) produced in Example 73, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 150 mg (yield 56.0 %) were obtained.

(0512)

NMR (CDCl3) delta: 1.14 (9H, s), 7.00 (1H, dd, J = 8 Hz, 2 Hz), 7.09 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.24-7.31 (3H, m), 7.33-7.39 (5H, m), 7.48-7.53 (3H, m), 7.68 (1H, dd, J = 8 Hz, 2 Hz), 7.83 (1H, d, J = 8 Hz), 8.00 (1H, dd, J = 8 Hz, 2 Hz), 8.18 (1H, br-s), 8.53 (1H, dd, J = 8 Hz, 2 Hz), 9.57 (1H, s), 10.25 (1H, s).

IR (ν, cm-1, KBr): 2212, 1704, 1658, 1582, 1558, 1532, 1472, 1442.

EI-MS (m/z, %): 551 (m +,49), 521 (30), 295 (100), 195 (48).

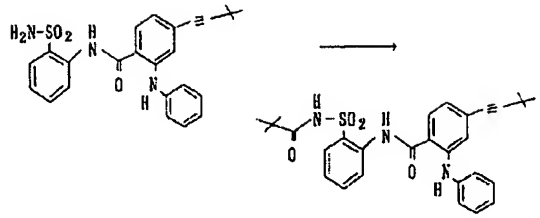
mp: 223-224 degrees.

(0513)

Example 80

N-(2-(4-(3,3-dimethyl butenyl)-2-phenylamino benzamide) benzensulphonyl) pivalamide.

(0514)



(0515)

Under a stream of nitrogen, pivaloyl chloride 0.06 ml (0.49 mmol) was added to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 110 mg (0.9 mmol) and 4-(3,3-dimethyl butenyl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 200 mg (0.45 mmol) produced in Example 70, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 180 mg (yield 75.0 %) were obtained.

(0516)

NMR (CDCl3) delta: 1.12 (9H, s), 1.38 (9H, s), 6.87 (1H, dd, J = 8 Hz, 2 Hz), 7.07 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.22-7.29 (3H, m), 7.32-7.38 (3H, m), 7.67 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.75 (1H, d, J = 8 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz),.8.15 (1H, br-s), 8.50 (1H, dd, J = 8 Hz, 2 Hz) 9.519 (1H, s), 10,17 (1H, s).

IR (ν, cm-1, KBr): 2224, 1714, 1652, 1594, 1580, 1564, 1530, 1498.

EI-MS (m/z, %): 531 (m +,85), 175 (100), 260 (53).

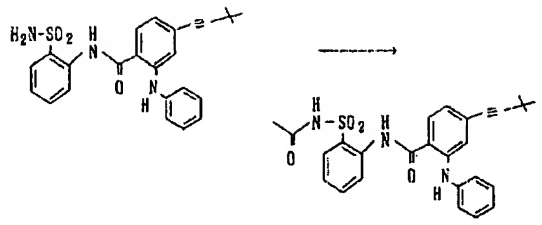
mp: 218-219 degrees.

(0517)

Example 81

N-(2-(4-(3,3-dimethyl butenyl)-2-phenylamino benzamide) benzensulphonyl) acetamide.

(0518)



(0519)

Acetic anhydride 0.07 ml (0.74 mmol) was added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 180 mg (1.47 mmol) and 4-(3,3-dimethyl butenyl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 300 mg (067 mmol) produced in Example 70, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 235 mg (yield 72.0 %) were obtained.

(0520)

NMR (CDCl3) delta: 1.28 (9H, s), 2.04 (3H, s), 6.85 (1H, dd, J = 8 Hz, 2 Hz), 7.07 (1H, dd, J = 8 Hz, 8 Hz), 7.22-7.29 (3H, m), 7.31-7.39 (3H, m), 7.66 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.73 (1H, d, J = 8 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz), 8.26 (1H, br-s), 8.55 (1H, dd, J = 8 Hz, 2 Hz) 9.49 (1H, s), 10,24 (1H, s).

IR (v, cm-1, KBr): 2224, 1730, 1658, 1582, 1556, 1538, 1498, 1470, 1442, 1418, 1336, 1270.

EI-MS (m/z, %): 489 (m +,73), 275 (100), 260 (70).

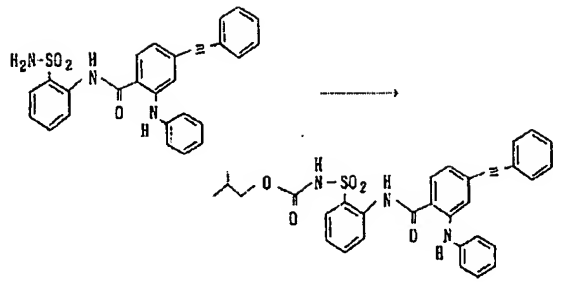
mp: 208-209 degrees.

(0521)

Example 82

N-(2-((2-methylpropyl oxycarbonyl amino) sulphonyl) phenyl) 2-phenylamino-4-phenyl-ethynyl benzamide.

(0522)



(0523)

Chlorocarbonic acid isobutyl ester 0.15 ml (1.18 mmol) was added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 289 mg (2.36 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 500 mg (1.07 mmol) produced in Example 73, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 455 mg (yield 75.0 %) were obtained.

(0524)

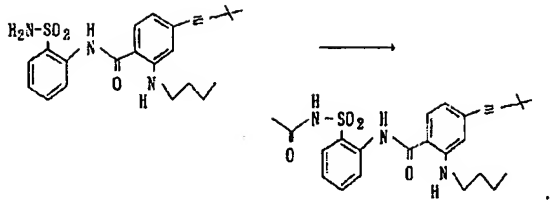
NMR (delta, CDCl3): 0.83 (6H, d, J = 7 Hz), 1.80-1.90 (1H, m), 3.85 (2H, d, J = 7 Hz), 6.98 (1H, dd, J = 8 Hz, 2 Hz), 7.10 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.24-7.31 (4H, m). 7.32-7.39 (4H, m), 7.47-7.55 (3H, m), 7.60 (1H, br-s), 7.68 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.76 (1H, d, J = 8 Hz), 8.03 (1H, dd, J = 8 Hz, 2 Hz), 8.61 (1H, dd, J = 8 Hz, 2 Hz), 9.57 (1H, s), 10.27 (1H, s).
IR (v, cm-1, KBr): 2212, 1716, 1674, 1582, 1556, 1516, 1472, 1424, 1356, 1226.
FAB-MS (m/z, %): 566 (M-H, 23), 265 (100).
mp: 155-156 degrees.

(0525)

Example 83

N-(2-(2-butylamino-4-(3,3-dimethyl butenyl) benzamide) benzensulphonyl) acetamide.

(0526)



(0527)

Acetic anhydride 0.07 ml (0.74 mmol) were added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 2-butylamino-4-(3,3-dimethyl butenyl)-N-(2-sulphamoyl phenyl) benzamide 300 mg (0.70 mmol) and 4-dimethylaminopyridine 189 mg (1.55 mmol), and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 250 mg (yield 76.0 %) were obtained.

(0528)

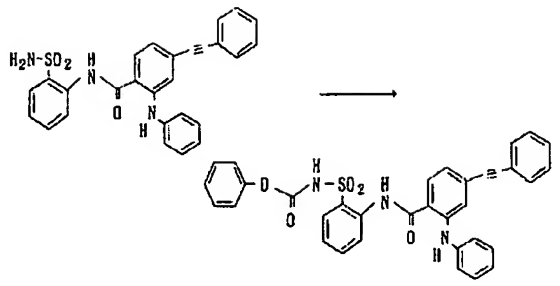
NMR (delta, CDCl3): 0.96 (3H, t, J = 7 Hz), 1.33 (9H, s), 1.44-1.56 (2H, m), 1.63-1.70 (2H, m), 2.04 (3H, s), 3.18 (2H, t, J = 7 Hz), 6.66 (1H, dd, J = 8 Hz, 2 Hz), 6.72 (1H, d, J = 2 Hz), 7.24 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.61 (1H, d, J = 8 Hz), 7.65 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.81 (1H, br-s), 8.01 (1H, dd, J = 8 Hz, 2 Hz), 8.20 (1H, br-s), 8.48 (1H, dd, J = 8 Hz, 1 Hz), 10.02 (1H, s).
IR (ν, cm-1, KBr): 3392, 3196, 2972, 2932, 2872, 2228, 1736, 1640, 1598, 1584, 1564, 1530, 1474, 1444, 1348, 1290, 1236, 1212, 1154, 854, 766.
EI-MS (m/z, %): 489 (m +,73), 275 (100), 260 (70).
mp: 155-156 degrees.

(0529)

Example 84

2-phenylamino-4-phenyl-ethynyl-N-(2-((phenyloxy carbonylamino) sulphonyl) phenyl) benzamide.

(0530)



(0531)

Chlorocarbonic acid phenyl 0.18 ml (1.42 mmol) was added under a stream of nitrogen to ethyl acetate (10 ml) solution of 4-dimethylaminopyridine 316 mg (2.60 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 548 mg (1.18 mmol) produced in Example 73, and it was stirred at room temperature for one hour. The reaction solution was washed successively with aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with ether, and title compound 520 mg (yield 75.0 %) were obtained.

(0532)

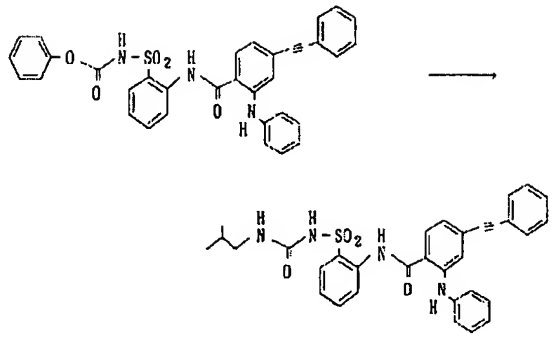
NMR (CDCl3) delta: 6.96 (1H, dd, J = 8 Hz, 2 Hz), 7,00-7.04 (2H, m), 7.11 (1H, dd, J = 8 Hz, 8 Hz), 7.18-7.38, (11H, m), 7.45 (1H, d, J = 2 Hz), 7.49-7.53 (2H, m), 7.68-7.74 (2H, m), 7.82 (1H, br-s), 8.09 (1H, dd, J = 8 Hz, 2 Hz), 8.63 (1H, dd, J = 8 Hz, 1 Hz), 9.50 (1H, s), 10.23 (1H, s).
IR (v, cm-1, KBr): 3392, 3064, 2864, 2216, 1748, 1646, 1582, 1560, 1528, 1498, 1476, 1442, 1420, 1360, 1320, 1288, 1226, 1198, 1162, 1128, 898, 754.
FAB-MS (m/z, %): 586 (M-H, 22), 451 (100).
mp: 146-147 degrees.

(0533)

Example 85

2-phenylamino-4-phenyl-ethynyl-N-(2-(((2-methylpropyl amino) carbonylamino) sulfonyl) phenyl) benzamide.

(0534)



(0535)

2-phenylamino-4-phenyl-ethynyl-N-(2-((phenyloxy carbonylamino) sulphonyl) phenyl) benzamide 105 mg (0.18 mmol) produced in Example 84 and benzene (5 ml) solution of isobutyl amine 0.04 ml (0.36 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 70 mg (yield 69.0 %) were obtained.

(0536)

NMR (CDCl3) delta: 0.83 (6H, d, J = 7 Hz), 1.64-1.71 (1H, m), 2.91 (2H, dd, J = 7 Hz, 6 Hz), 6.23 (1H, br-s), 6.94 (1H, dd, J = 8 Hz, 2 Hz), 7.10 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.21-7.28 (3H, m), 7.32-7.40 (5H, m), 7.45 (1H, d, J = 2 Hz), 7.48-7.53 (2H, m), 7.66 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.69 (1H, d, J = 8 Hz), 7.88 (1H, dd, J = 8 Hz, 2 Hz), 8.36 (1H, br-s), 8.56 (1H, dd, J = 8 Hz, 1 Hz), 9.56 (1H, s), 10.00 (1H, s).

IR (v, cm-1, KBr): 3392, 3268, 3064, 2960, 2932, 2220, 1682, 1658, 1580, 1554, 1530, 1498, 1472, 1442, 1418, 1344, 1320, 1288, 1224, 1152, 752.

FAB-MS (m/z, %): 565 (M-H, 16), 265 (100).

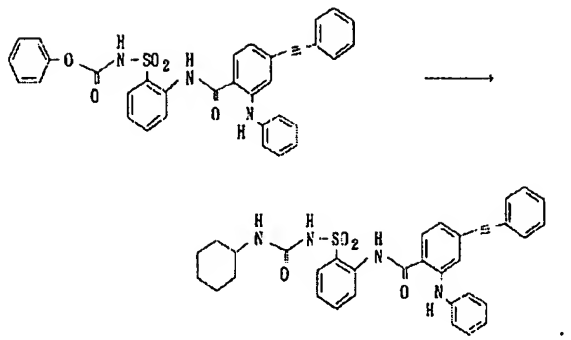
mp: 183-184 degrees.

(0537)

Example 86

N-(2-(((cyclohexyl amino) carbonylamino) sulfonyl) phenyl) 2-phenylamino-4-phenyl-ethynyl benzamide.

(0538)



(0539)

2-phenylamino-4-phenyl-ethynyl-N-(2-((phenyloxy carbonylamino) sulphonyl) phenyl) benzamide 200 mg (0.34 mmol) produced in Example 84 and benzene (5 ml) solution of cyclohexylamine 0.09 ml (0.75 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic. acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 136 mg (yield 67.0 %) were obtained.

(0540)

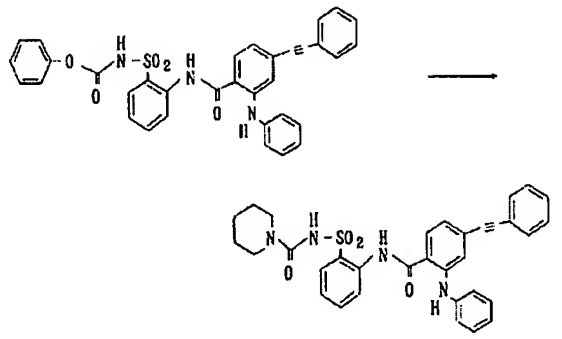
NMR (delta, CDCl3): 1.06 (2H, m), 1.20-1.28 (2H, m), 1.45-1.70 (4H, m), 1.75-1.85 (2H, m), 3.45-3.55 (1H, m), 6.00 (1H, br-s), 6.96 (1H, dd, J = 8 Hz, 2 Hz), 7.11 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.24-7.30 (5H, m), 7.32-7.40 (4H, m), 7.46 (1H, d, J = 2 Hz), 7.49-7.53 (2H, m), 7.64-7.74 (3H, m), 7.89 (1H dd, J = 8 Hz, 2 Hz), 8.57 (1H, dd, J = 8 Hz, 1 Hz), 9.55 (1H, s), 10.03 (1H, s).
IR (ν, cm-1, KBr): 3400, 3316, 3240, 2940, 2856, 2212, 1686, 1662, 1584, 1556, 1530, 1498, 1470, 1444, 1422, 1338, 1284, 1252, 1218, 1154, 1128, 1028, 756.
FAB-MS (m/z, %): 591 (M-H, 9), 311 (100).
mp: 188-189 degrees.

(0541)

Example 87

2-phenylamino-4-phenyl-ethynyl-N-(2-((piperidino carbonylamino) sulfonyl) phenyl) benzamide.

(0542)



(0543)

2-phenylamino-4-phenyl-ethynyl-N-(2-((phenyloxy carbonylamino) sulphonyl) phenyl) benzamide 200 mg (0.34 mmol) produced in Example 84 and benzene (5 ml) solution of piperidine 0.07 ml (0.75 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 94 mg (yield 50.0 %) were obtained.

(0544)

NMR (delta, CDCl3): 1.55 (6H, br-s), 3.32 (4H, br-s), 6.98 (1H, dd, J = 8 Hz, 2 Hz), 7.08 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.24-7.30 (5H, m), 7,31-7.39 (4H, m), 7.47-7.57 (3H, m), 7.64 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.90 (1H, d, J = 8 Hz), 8.00 (1H, dd, J = 8 Hz, 2 Hz), 8.49 (1H, dd, J = 8 Hz, 1 Hz), 9.64 (1H, s), 10.53 (1H, s).

IR (ν, cm-1, KBr): 3268, 2940, 2860, 2212, 1682, 1660, 1582, 1562, 1536, 1498, 1478, 1442, 1422, 1316, 1286, 1256, 1228, 1160,752.

FAB-MS (m/z, %): 577 (M-H, 100), 265 (66).

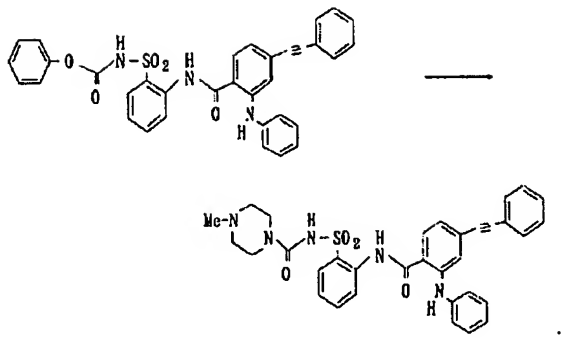
mp: 163-164 degrees.

(0545)

Example 88

N-(2-(((4-methyl piperazinyl) carbonylamino) sulfonyl) phenyl) 2-phenylamino-4-phenyl-ethynyl benzamide.

(0546)



(0547)

2-phenylamino-4-phenyl-ethynyl-N-(2-((phenyloxy carbonylamino) sulphonyl) phenyl) benzamide 160 mg (0.27 mmol) produced in Example 84 and benzene (5 ml) solution of 1-methylpiperazine 0.07 ml (0.75 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 130 mg (yield 81.0 %) were obtained.

(0548)

NMR (delta, CDCl3): 2.23 (4H, br-s), 3.44 (4H, br-s), 6.84 (1H, d, J = 8 Hz), 6.94-7.04 (2H, m), 7.16 (2H, d, J = 8 Hz), 7.21-7.30 (6H, m), 7.34-7.44 (4H, m), 7.76 (1H, d, J = 8 Hz), 7.93 (1H, br-s), 8.33 (1H, d, J = 8 Hz), 9.56 (1H, s), 10.39 (1H, s).

IR (ν, cm-1, KBr): 3316, 3056, 2940, 2856, 2800, 2212, 1660, 1590, 1556, 1536, 1498, 1464, 1442, 1420, 1320, 1292, 1266, 1226, 1142, 1106,756.

FAB-MS (m/z, %): 592 (M-H, 62), 197 (100).

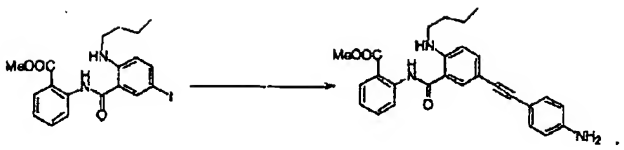
mp: 181-182 degrees.

(0549)

Reference Example 44

2-((4-amino) phenyl-ethynyl-2-butylamino benzamide) methyl benzoate ester.

(0550)



(0551)

4-ethynyl aniline 200 mg (1.72 mmol), dichlorobis triphenylphosphine palladium 23 mg (0.03 mmol) and copper iodide 12 mg (0.06 mmol) were added to mixed solution of diethylamine (12 ml) of 2-(2-butylamino-5-iodobenzamide) methyl benzoate 300 mg (0.66 mmol) and tetrahydrofuran (5 ml), and the mixture was stirred at room temperature for 20 hours, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 270 mg (yield 92.6 %) were obtained.

(0552)

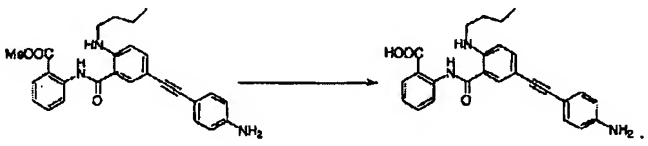
NMR (delta, CDCl3): 0.97 (3H, t, J = 7 Hz), 1.42-1.52 (2H, m), 1.64-1.72 (2H, m), 3.18-3.22 (2H, m), 3.78 (2H, s), 3.97 (3H, s), 6.63 (2H, d, J = 8 Hz), 6.68 (1H, d, J = 9 Hz), 7.08-7.14 (1H, m), 7.33 (2H, d, J = 8 Hz), 7.46 (1H, dd, J = 9.2 Hz), 7.55-7.61 (1H, m), 7.88 (1H, d, J = 2 Hz), 7.95 (1H, t, J = 5 Hz), 8.07 (1H, dd, J = 8.1 Hz), 8.66-8.72 (1H, d, J = 8 Hz), 11.71 (1H, s).

(0553)

Example 89

2-((4-amino) phenyl-ethynyl-2-butylamino benzamide) benzoic acid.

(0554)



(0555)

1M-sodium hydroxide solution 3 ml were added to dioxane (20 ml) solution of 2-((4-amino) phenyl-ethynyl-2-butylamino benzamide) methyl benzoate 270 mg (0.61 mmol) produced in Reference

Example 44, and the mixture was stirred at room temperature for 24 hours. 1M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 170 mg (yield 65.2 %) were obtained.

(0556)

NMR (delta, CDCl3): 0.98 (3H, t, J = 7 Hz), 1.43-1.54 (2H, m), 1.64-1.74 (2H, m), 3.21 (2H, t, J = 7 Hz), 6.57 (2H, d, J = 8 Hz), 6.69 (1H, d, J = 9 Hz), 6.97-7.04 (1H, m), 7.33 (2H, d, J = 8 Hz), 7.47 (1H, dd, J = 9.2 Hz), 7.57-7.64 (1H, m), 7.88 (1H, d, J = 2 Hz), 8.01 (1H, dd, J = 8.1 Hz), 8.78 (1H, d, J = 8 Hz), 11.68 (1H, s).

IR (v, cm-1, KBr): 3396, 1652, 1592, 1528, 1224,764.

FAB-MS (m/z, %): 426 (M-H, 100).

mp: 190 degradation.

(0557)

Reference Example 45

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0558)

(0559)

Thionyl chloride 2.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene (20 ml) solution of 2-chloro-5-phenyl-ethynyl benzoic acid 2.8 g (10.91 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of potassium carbonate 2.3 g (16.36 mmol), water (20 ml) of 2-ethyl aminobenzoic acid 1.6 ml (10.91 mmol) and ethyl acetate (10), and it was stirred at room temperature for 18 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 4.12 g (yield 93.5 %) were obtained.

(0560)

NMR (delta, CDCl3): 1.40 (3H, t, J = 7 Hz), 4.37 (2H, q, J = 7 Hz), 7.14-7.20 (1H, m) 7.34-7.40 (3H, m), 7.45 (1H, d, J = 8 Hz), 7.50-7.58 (3H, m), 7.60-7.66 (1H, m), 7.80 (1H, d, J = 2 Hz), 8.10 (1H, dd, J = 8.1 Hz), 8.88 (1H, d, J = 8 Hz), 11.57 (1H, s).

(0561)

Reference Example 46

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid.

(0562)

(0563)

1M-sodium hydroxide solution 30 ml were added to ethanol (20 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 4.12 g (10.20 mmol) produced in Reference Example 45, and the mixture was heated under reflux for three hours. 1M-concentrated hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 3.26 g (yield 85.0 %) were obtained.

(0564)

NMR (delta, CDCl3): 7.14-7.20 (1H, m), 7.33-7.38 (1H, d, J = 8 Hz), 7.50-7.58 (3H, m), 7.64-7.70 (1H, m), 7.81 (1H, d, J = 2 Hz), 8.12 (1H, dd, J = 8.1 Hz), 8.98 (1H, d, J = 8 Hz), 11.39 (1H, s).

(0565)

Example 90

2-((2-dimethylamino) ethylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0566)

(0567)

Potassium carbonate 0.40 g (2.87 mmol) and 5 wt.% activated copper was added to N, N-dimethylethylenediamine (8 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.90 g (2.39 mmol) produced in Reference Example 46, and it was heated with stirring at 180 degrees in sealed tube for three hours and next it was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.42 g (yield 41.1 %) were obtained.

(0568)

NMR (delta, DMSO-d6): 2.83 (6H, s), 3.29 (2H, t, J = 7 Hz), 3.64-3.74 (2H, m), 6.98 (1H, d, J = 9 Hz), 7.19-7.26 (1H, m), 7.40-7.46 (3H, m), 7.49-7.55 (2H, m), 7.58 (1H, dd, J = 9.2 Hz), 7.62-7.68 (1H, m), 7.91 (1H, d, J = 2 Hz), 7.94-8.00 (1H, m), 8.04 (1H, dd, J = 8.1 Hz), 8.53 (1H, d, J = 8 Hz), 11.98 (1H, s).

IR (ν, cm-1, KBr): 2208, 1680, 1660, 1592, 1530, 1228,754

FAB-MS (m/z, %): 426 (M-H, 100).

mp: 181-183 degrees.

(0569)

Pharmacological Test 1

Measurement of ACC inhibiting activity

1. Purification of ACC.

12 week old male SD series rats were fasted for two days, and thereafter, high sucrose food (67 % sucrose, 17.1 % casein, 9.8 % cellulose, 5 % salt, 0.1 % choline chloride, 1 % vitamins) was given for two days, and decapitation under ether anaesthesia and bleeding were carried out, next liver was quickly removed. This liver was diced in ice cooled buffer A (225 mM mannitol, 75 mM sucrose, 10 mM Tris / HCl [pH 7.5], 0.05 mM EDTA-2Na, 5 mM potassium citrate, 2.5 mM MnCl2, 10 mg/l

aprotinin, 10 mg/l leupeptin, 10 mg/l antitrypsin), and water content was eliminated, thereafter buffer A was added so as to become 5 ml/g, and it was homogenised with Polytron homogenizer for four minutes. This was centrifuged and separated at 1,000 g for ten minutes and next supernatant was centrifuged at high speed at 17,000 g for ten minutes and was separated.

(0570)

Ammonium sulphate was added so as to form 35 %, and the obtained supernatant was stirred for 45 minutes and it was centrifuged at high speed at 17,000 g for ten minutes and was separated. Buffer B of 100 ml (100 mM Tris / HCl [pH 7.5], 0.5 M NaCl, 1 mM EDTA-2Na, 0.1 mM DTT, 10 % glycerol, 10 mg/l aprotinin, 10 mg/l leupeptin, 10 mg/l antitrypsin) was added to the obtained precipitation, and it was ultracentrifuged and separated at 40,000 g for 20 minutes, supernatant was dialysed overnight with buffer C of 150 fold volume (100 mM Tris / HCl [pH 7.5], 0.5M NaCl, 1 mM EDTA-2Na, 0.1 mM DTT, 10 % glycerol), and filtration was carried out with filter of 5 μM. Filtrate was applied to biotin affinity column and was washed with buffer B, and thereafter, ACC was eluted with buffer B which included 5 mM biotin.

(0571)

2. Measurement of ACC inhibiting activity

Compounds produced in aforesaid Examples were each dissolved in DMSO, and introduced into glass vials, and reagent 1 containing 250 μl ACC (40 mM Tris / HCl [pH 7.5], 40 mM MgCl2, 40 mM sodium citrate, 2 mM DTT, 100 μg/ml fatty acid free BSA) was added, and it was warmed in a thermostat bath at 37 degrees for 30 minutes. After ice cooling, reagent 2 of 250 μl (40 mM Tris / HCl [pH 7.5], 2 mM DTT, 8 mM ATP, 0.5 mM acetyl CoA) containing NaH[14]CO3 of 74 kBq was added, and further it was warmed in a thermostat bath at 37 degrees for ten minutes, and next 1N-HCl of 0.1 ml was added, and reaction was stopped. Water content in glass vial was completely eliminated under reduced pressure, and emulsification scintillator (Cleasol I) was added to the glass vial, and radioactivity of 14C was measured using liquid scintillation counter. Inhibition activity of each compound (5.6 x 10[-6] mol) was determined. The results thereof are shown in Table 1.

(0572)

Pharmacological Test 2

Measurement of inhibiting activity (FA biosynthesis inhibiting activity) with respect to fatty acid synthesis in cell

Compounds produced in aforesaid Examples were each dissolved using DMSO and was added to experiment culture medium (DMEM, 0.05 μg/ml Insulin, 0.1 mg/ml glucose, 18.5 kBq/ml (14C)-

glucose). It was prepared to form 0.75 x 10 [6] cells/ml. Moreover, HepG2 cells were inoculated by 1 ml/well in 12-well plate, and it was cultured overnight (culture solution: DMEM, 4.5 g/ml, glucose, 10 % FBS), at 5 % CO2, 37 deg C, thereafter the cells were washed twice with PBS (-) buffer, and next experiment culture medium was added by 0.5 ml/well, and it was cultured at 5 % CO2, 37 deg C for three hours. After culturing, the cells were washed twice with ice cooled PBS (-) buffer, and lipid of the cells which were scraped off was extracted with lipid extraction liquid (chloroform : methanol = 2:1). Ethanol 2.5 ml and 33 % potassium hydroxide 0.1 ml were added to the extract, and it was placed on a water bath at 70 degrees for one hour. Lipid was extracted from this reactant again, and extract was applied to silica gel thin layer plate. This was developed using developing solution (hexane : diethyl ether : acetic acid = 80:20:1), and thereafter, iodine colouring site of fatty acid was collected, and radioactivity thereof was measured using liquid scintillation counter. Inhibiting activity % of each compound (3.0 x 10 [-5] M) was determined. The results thereof are shown in Table 1.

(0573)

(Table 1)

Ex. No.	Compound name	ACC inhibition activity (%) (5.6×10^{-6} M)	FA synthesis inhibition (%) (3.0×10^{-5} M)
7	2-(4-benzyloxy-2-phenylaminobenzamide) benzoic acid	22.8	92.3
8	2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid	53.7	76.2
9	2-[4-pheylethynyl-2-(3-trifluoromethylphenylamino) benzamide] benzoic acid	61.3	66.5
15	2-(2-hexylamino-4-phenylethynylbenzamide) benzoic acid	40.2	66.5
16	2-(2-benzylamino-4-phenylethynylbenzamide) benzoic acid	57.8	51.2
21	2-(2-n-octylaminobenzamide) benzoic acid	41.5	37.2
22	2-(2-n-decylaminobenzamide) benzoic acid	37.3	36.0
30	2-(2,6-dihexylaminobenzamide) benzoic acid	38.4	91.6
31	2-[4-phenylethynyl-2-(3-phenylpropylamino) benzamide] benzoic acid	93.7	50.5
33	2-(2-butylamino-4-phenylethynylbenzamide) benzoic acid	69.0	54.9
35	2-[5-phenylethynyl-2-(3-phenylpropyl) aminobenzamide benzoic acid	69.0	54.9
36	2-(2-phenylamino-5-phenylethynylbenzamide) benzoic acid	87.8	82.8
37	2-(2-methylamino-4-phenylethynylbenzamide) benzoic acid	41.7	78.6

(0574)

(Table 2)

Ex. No.	Compound name	ACC inhibition activity (%) (5.6×10^{-6} M)	FA synthesis inhibition (%) (3.0×10^{-5} M)
40	2-[2-butylamino-5-(4-nitrophenyl) ethynylbenzamide] benzoic acid	69.9	80.5
41	2-[2-butylamino-5-(4-cyanophenyl) ethynylbenzamide] benzoic acid	80.5	85.3
42	2-[2-butylamino-5-(4-hydroxyphenyl) ethynylbenzamide] benzoic acid	92.5	54.7
43	2-(2-methylamino-5-phenylethynylbenzamide) benzoic acid	79.0	97.3
44	2-(2-ethylamino-5-phenylethynylbenzamide) benzoic acid	86.5	98.3
45	2-(2-propylamino-5-phenylethynylbenzamide) benzoic acid	87.6	95.0
46	2-(2-butylamino-5-phenylethynylbenzamide) benzoic acid	79.8	85.7
47	5-chloro-2-(4-benzyloxy-2-phenylaminobenzamide) benzoic acid	73.1	77.6
49	3-(4-benzyloxy-2-phenylaminobenzamide)-2-naphthalene carboxylic acid	75.2	56.6
52	2-(4-benzyloxy-2-phenylaminobenzamide)-5-hydroxy benzoic acid	49.4	25.5
53	5-chloro-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid	84.1	64.4
55	3-(2-phenylamino-4-phenylethynylbenzamide)-2-naphthalene carboxylic acid	58.9	42.4

(0575)

(Table 3).

Ex. No.	Compound name	ACC inhibition activity (%) (5.6×10^{-6} M)	FA synthesis inhibition (%) (3.0×10^{-5} M)
55	5-methoxy-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid	76.3	53.6
57	5-methyl-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid	78.0	67.6
59	3-(2-phenylamino-4-phenylethynylbenzamide) thiophene benzoic acid	55.1	85.3
60	5-bromo-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid	82.2	67.1
61	1-(2-phenylamino-4-phenylethynylbenzamide) cyclohexane carboxylic acid	30.0	70.3
62	2-[4-(octan-1-yl)-2-phenylaminophenylamino benzamide] benzoic acid	67.4	70.2
63	2-[4-(3,3-dimethylbutynyl)-2-phenylamino benzamide] benzoic acid	80.7	87.0
64	2-[2-phenylamino-4-(bentan-1-yl) benzamide benzoic acid	74.1	87.2
65	2-[2-butylamino-4-(3,3-dimethylbutynyl) benzamide] benzoic acid	48.5	59.6
66	2-[2-butylamino-5-(2-pyridylethynyl) benzamide] benzoic acid	47.8	72.2
67	2-[2-butylamino-5-(2-thiophenylethynyl) benzamide] benzoic acid	56.7	65.6
74	N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] benzamide	52.9	58.6

(0576)

(Table 4).

Ex. No.	Compound name	ACC inhibition activity (%) (5.6×10^{-6} M)	FA synthesis inhibition (%) (3.0×10^{-5} M)
75	N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl]-4-trifluoromethylbenzamide	26.0	14.6
76	N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] acetamide	87.5	69.4
77	N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] hexanamide	88.1	84.9
78	N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] decanamide	59.5	19.7
79	N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] pivalamide	83.7	64.9
80	N-[2-[4-(3,3-dimethylbutynyl)-phenylaminobenzamide] benzenesulphonyl] pivalamide	87.5	69.4
81	N-[2-[4-(3,3-dimethylbutynyl)-phenylaminobenzamide] benzenesulphonyl] acetamide	28.0	84.4
82	N-[2-[(2-methylproyloxycarbonylamino) sulphonyl] phenyl] 2-phenylamino-4-phenylethynylbenzamide	91.9	67.2

(0577)

Advantages Afforded by this Invention

As described above, this invention puts forward novel aromatic amide derivatives represented by the above-mentioned general formula (I) as effective ACC activity inhibiting agent in therapy of visceral fat syndrome which is a risk factor of geriatric diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like, and effect on medical care thereof is great.

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